ICS medal and research abstract presentations

Research Gold Medal Presentations winner

TNF receptors in experimental acute lung injury – a double-edged sword

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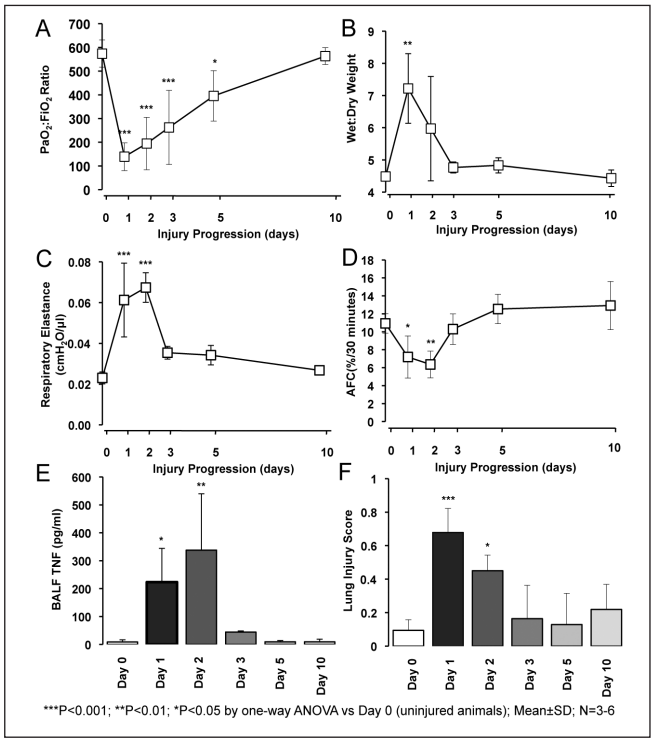
Tumour necrosis factor (TNF) is a pleiotropic cytokine strongly implicated in acute lung injury/acute respiratory distress syndrome (ALI/ARDS), but there still remains considerable controversy as to its precise roles. TNF signals through two receptors – TNF receptor 1 (p55) and TNF receptor 2 (p75). It has been well established that both TNF receptors initiate distinct signalling pathways and hence, different cellular responses.[1] We have previously shown that the two TNF receptors have distinct responses in pulmonary oedema formation in a model of ventilator induced ALI,[2] and furthermore that selective intra-alveolar p55 TNF receptor blockade using novel domain antibody technology reduces this oedema.[3] This work focuses on understanding the underlying pathophysiological mechanisms, but more importantly, on investigating the impact of TNF receptors in more clinically relevant scenarios.



Funding: National Institute of Academic Anaesthesia and the Wellcome Trust

Hydrochloric acid (50µL, 0.15M) was administered intratracheally into anaesthetised wild type (WT) C57BL6 mice, or mice lacking p55 (p55KO) or p75 (p75KO) receptors. They were mechanically ventilated over a three-hour protocol, as previously described,[4,5] and alveolar oedema, inflammation and fluid clearance (AFC) rate was measured to ascertain severity of alveolar epithelial damage.

P55KO animals had significantly attenuated physiological parameters of lung injury compared to WT injured animals (see **Table**). We found p55KO animals showed improved alveolar epithelial function with reduced sRAGE levels in the bronchoalveolar lavage fluid (BALF) and higher AFC rates. P75KO animals showed worse respiratory mechanics and alveolar inflammation.

We have shown that the two TNF receptors lead to opposing effects and provide the first mechanistic insight into the critical role of the p55 TNF receptor in promoting alveolar epithelial cell dysfunction during the first few hours of experimental ALI/ARDS. Importantly, this study provides a rationale for the application of specific p55 TNF receptor blocking strategies for the prevention and resolution of alveolar oedema in clinical ALI/ARDS.

	WT uninjured	WT acid	p55KO acid	p75KO acid
Change in respiratory elastance (%)	29.7±8.9	105±33#	50±20*	166±52*
Final PaO_2 (mm Hg)	438±31	156±70#	392±64*	149±79
Lung wet:dry weight	5.0±0.5	6.9±0.5#	5.6±0.5*	7.1±1.0
BALF protein (mg/mL)	0.5±0.3	2.0±0.4#	1.0±0.2*	1.9±0.7
BALF IL-6 (pg/ml=L)	169±50	2763±405#	2418±389	4346±1221*
BALF RAGE (ng/mL)	2.7±2.1	83.3±37.8#	42.9±23.5*	90.6±25.5
AFC (%/30 minutes)	10.95±0.97	5.62±2.29#	8.09±1.33*	6.24±2.25

mean±SD; #p<0.01 *vs* WT uninjured; *p<0.05 *vs* WT acid; n=4-10

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Research Gold Medal Presentations

Pulmonary neutrophil kinetics: new insights into the pathogenesis of ARDS

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Studies in humans and animals have suggested that there is a substantial pool of neutrophils within the lung under physiological conditions. Such studies, however, are susceptible to *ex vivo* neutrophil injury during cell purification and labelling, which results in major alterations in neutrophil rheology and behaviour when re-injected. Neutrophil priming is a pre-requisite for neutrophil-mediated tissue injury and hence the development of ARDS, but little is known about the effects of priming on neutrophil kinetics.

The pulmonary transit of bolus-injected autologous radio-labelled neutrophils was studied using two independent methods: rapid sequence scintigraphy of the thorax and arterial outflow detection.

Neutrophils isolated and radio-labelled in the presence of autologous plasma passed through healthy human lungs with a transit time of 14.2±0.3 seconds (n=8), only 2.7±1.0 seconds, more slowly than erythrocytes and with <5% first-pass pulmonary retention (n=6). Furthermore, 100% of neutrophils primed with GM-CSF prior to re-injection were retained on first-pass transit through the lung, with a slow linear washout leaving 50% still retained at 40 minutes (n=8). Cells primed with PAF were initially retained within the lung, as seen with GM-CSF, but thereafter eluted much faster, so that within 30 minutes there was no detectable pulmonary retention of neutrophils (n=6).

These findings contradict previous animal and human studies, which suggest that there is a substantial pool of neutrophils within the lung under physiological conditions. In addition, this work provides the first evidence that neutrophil priming alters dramatically the pulmonary transit of these

cells and that de-priming of neutrophils is an in vivo phenomenon. This latter finding supports the novel hypothesis that the pulmonary vasculature serves the important function of extracting primed cells from the circulation, allowing them to de-prime and later releasing them in a quiescent state, and that a key step in the pathogenesis of ARDS may be failure of the pulmonary de-priming mechanism.

Strategies to improve quality of cardiopulmonary resuscitation

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Each year many people die prematurely from cardiac arrests.[1,2] High quality cardiopulmonary resuscitation (CPR) leads to improved patient outcome, but the quality of CPR is often poor in the clinical setting.[5-7] A programme of research was carried out to explore strategies that can improve the quality of CPR.

Performing chest compression of adequate depth has been shown to improve patient outcome.[8] There is some evidence to support the use of feedback/prompt devices in both training and the clinical setting.[9]

This randomised controlled trial compared three devices: CPREzy™ (pressure-sensing device), Phillips MRX Q-CPR defibrillator (accelerometer device) and metronome; against a control group. CPREzy significantly increase compression depth (37.24 mm *vs* 43.64 mm, p=0.02) and reduced the proportion of compressions with inadequate depth (0.52 *vs* 0.24, p=0.013). Metronome had no effect on depth (39.88 mm *vs* 40.64 mm, p=0.802). QCPR significantly decreased compression depth from 37.38 mm to 33.19 mm (p=0.04) and increased the proportions of compressions with inadequate depth (0.54 *vs* 0.82, p=0.068). Not all feedback devices led to improved chest compression performance. Users should recognise device limitations and adjust their techniques accordingly.

In crisis situations team leadership skills are essential for effective task performance. A simulation study was carried out to examine the relationship between team leadership and quality of CPR. Forty participants were asked to lead a cardiac arrest team. Their performance was scored using the CASTest score[11] and Leadership Behaviour Description Questionnaire (LBDQ)[12] for leadership skills.

Good leadership skills were associated with significantly better overall technical performance (R^2 Linear=0.752, p<0.001). Leaders with better leadership skills was quicker to defibrillate (p=0.001), have shorter pre-shock pauses (p=0.002) and lower no flow ratio (p=0.057). The results strongly support more training in effective leadership in resuscitation.

Some roles traditionally performed by doctors are now extended to the multi-professional team. An observational study was carried out to compare how professional background of team leader (advanced care practitioners, ACP and doctors, DR) affects the quality of CPR.

One hundred and ninety-four cardiac arrests were analysed. No significant difference was found in no flow ratio (DR 19% *vs* ACP 16%, p=0.944), compression depth (DR 43.37±11.9 mm *vs* ACP 41.27 ±12.5 mm, p=0.366) or proportion of compressions with depth <38 mm (DR 0.17 *vs* ACP 0.27, p=0.233). Professional background of team leader did not affect quality of CPR or patient outcome.

Intubation with endotracheal tube (ETT) was considered the gold standard of securing a patient's airway during resuscitation. However, intubation attempts can cause serious complications.[13-15] Supraglottic airway devices such as laryngeal mask airway (LMA) have been advocated as an alternative.[16]

An observational study of 100 consecutive patients requiring CPR was carried out to compare quality of CPR data before and after airway insertion to investigate the impact of airway device. Both ETT and LMA significantly reduce no flow ratio (NFR) (ETT from 0.24 (0.17, 0.40) to 0.15 (0.09, 0.28), p=0.012, LMA from 0.28 (0.23, 0.40) to 0.13 (0.11, 0.19), p=0.0001). No significant difference in quality of CPR was found between airway groups. LMA was quicker to insert. The results support the use of LMA during cardiac arrest especially when expertise in intubation is not available.

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Biomarkers in the site-specific diagnosis of ventilator-associated pneumonia

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The diagnosis of VAP and search for useful biomarkers remain challenging. Firstly, no gold standard exists for VAP diagnosis. Second, blood-borne biomarkers are not discriminatory in multi-site infections. Third, soluble proteins in BAL fluid are subject to dilutional correction. Furthemore, the dynamic flux of cell-surface and cleaved soluble markers questions the meaning of isolated soluble marker concentrations. Finally, multiple organ-isms cause VAP. Thus, standalone soluble biomarkers are unlikely to be useful.

We addressed these concerns for identifying putative VAP biomarkers, by including patients with a strong likelihood of VAP presence or absence. Excluding those with intermediate probability reduced reclassification bias. Quantifying cell-surface biomarkers using flow-cytometry avoided dilutional bias. TREM-1 (triggering receptor expressed on myeloid cells-1) is implicated in infection pathways, particularly pulmonary. As cell-surface TREM-1 co-exists with its soluble counterpart, we sampled both simultaneously, with other cell and soluble markers. We investigated whether the BAL/blood ratio improved diagnostic accuracy further, differentiated site of infection and corrected for variable blood levels. We identified biomarkers with potential diagnostic utility from a derivation cohort then validated a diagnostically accurate panel.

In a prospective study of 91 patients, BAL monocytic surface TREM-1 (mTREM-1) was significantly elevated in VAP. The BAL/blood ratio improved diagnostic accuracy further and differentiated pulmonary from non-pulmonary sepsis. A validated biomarker panel comprising six surface and soluble analytes had an AUC of 0.98 and diagnostic accuracy of near 90% for VAP. The kinetic levels of BAL mTREM-1 rose with infection and fell with resolution, confirming its potential as a diagnostic and monitoring biomarker.

In conclusion, TREM-1, with other cell-surface proteins and the BAL/blood ratio can facilitate VAP diagnosis and differentiate

pulmonary from non-pulmonary infection. An approach of simultaneous sampling may improve clinically relevant VAP definitions. Future studies should test this biomarker panel, in a multicentre study of patients with suspected VAP.

Novel pharmacological therapies in models of acute lung injury

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Despite multiple phase 3 clinical trials, there are no proven pharmacological therapies to reduce mortality in acute lung injury (ALI). There is a need for clinically relevant human models of ALI to test novel therapies to provide mechanistic data to support and inform the design of subsequent clinical trial in ALI.

Previous studies have shown that lipopolysaccharide (LPS) inhalation in normal volunteers causes alveolar and systemic inflammation qualitatively similar to ALI and is safe.[1] However, the effect of inhaled LPS on cell specific markers of alveolar injury is unknown. ALI occurs in 10-20% patients undergoing oesophagectomy and with a mortality of up to 50%.[2,3] Subclinical lung injury evidenced by increased endothelial permeability[4] and a fall in exhaled breathe condensate (EBC) pH[5] reflecting alveolar inflammation has been demonstrated in patients following one lung ventilation.

Simvastatin modulates a number of inflammatory processes described in ALI *in vitro* and in animal models of ALI.[6,7] Keratinocyte growth factor (KGF) modulates a variety of mechanisms recognised to be important in alveolar repair *in vitro* and in animal models of ALI.[8,9]

The objectives of my research were to;

1. Establish inhaled LPS as a model of ALI.
2. Investigate the effect of simvastatin in the inhaled LPS model of ALI.
3. Investigate the effect of simvastatin on physiological and biological outcomes in patients undergoing oesophagectomy.
4. Investigate the effect of KGF *in vitro* and in the inhaled LPS model of ALI

Data are mean (SD) or median (IQR) as appropriate. Continuous data were analysed by unpaired t test or Mann Whitney U test and categorical data using Fisher's exact test as appropriate.

Inhaled LPS as a model of ALI

Subjects inhaled 50µg LPS. BAL and blood were collected at 6 hr and 24 hr respectively post LPS inhalation. To explore the effects of LPS on the epithelial-endothelial barrier, biomarkers in BAL and plasma of subjects enrolled in the placebo arm of a clinical trial studying the effects of simvastatin (ISRCTN21056528) in the inhaled LPS model, were compared against five healthy volunteers who did not inhale LPS.

We have confirmed that inhaled LPS inhalation induces a qualitatively similar inflammatory response to ALI. Further we have for the first time found that LPS inhalation causes self-limiting epithelial (reduced BAL surfactant Protein D; SP-D) and endothelial injury (increased BAL von Willebrand factor) with increase in protein permeability reflecting alveolar barrier dysfunction supporting LPS inhalation as a model of ALI.

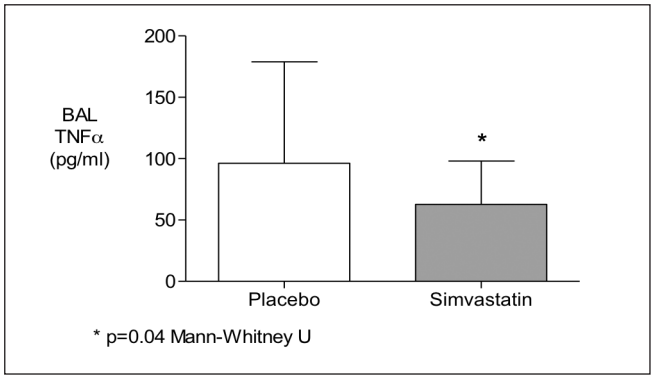

Figure 1. Anti-inflammatory effect of simvastatin in inhaled LPS model of ALI.

Effects of simvastatin in inhaled LPS model of ALI

A randomised double blind allocation concealed placebo controlled trial (ISRCTN21056528) was conducted investigating the effects of simvastatin 40 mg, simvastatin 80 mg or placebo (1:1:1) for four days prior to LPS inhalation. In this study we found simvastatin had pulmonary and systemic anti-inflammatory effects (**Figure 1**) associated with increased neutrophilic apoptosis and reduced NFκB activation.[1]

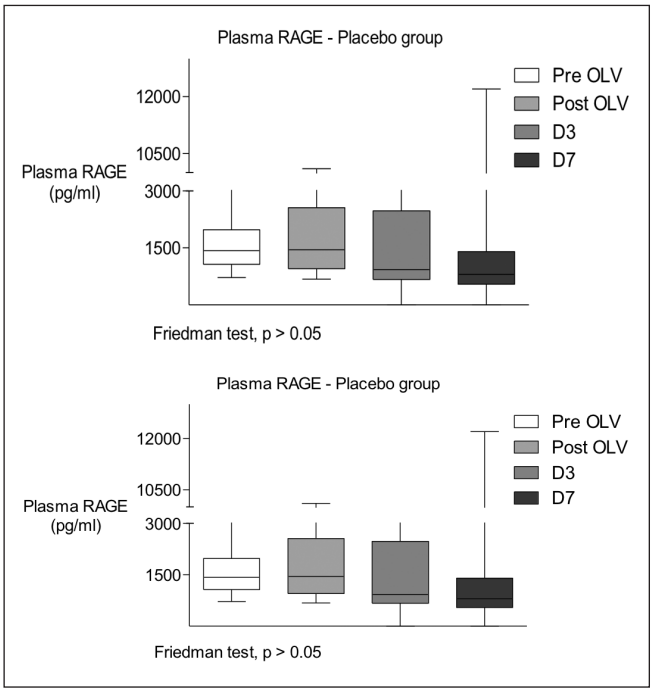

Figure 2. Simvastatin pre-treatment attenuates alveolar type I epithelial cell injury after one lung ventilation.

Effects on simvastatin on lung injury in a one lung ventilation (OLV) model of ALI

A randomised double blind allocation concealed placebo controlled trial (ISRCTN56543987) was undertaken in patients undergoing oesphagectomy to investigate the effect of simvastatin 80 mg or placebo enterally for four days prior to surgery and for seven days post-operatively. Markers of inflammation including plasma cytokines and intra-operative EBC pH, as a marker of alveolar inflammation, alveolar epithelial injury (plasma Receptor for Advanced Glycation End-products; RAGE) (**Figure 2**, previous page) and systemic endothelial function (urine albumin creatinine ratio; ACR) were measured.

Simvastatin pre-treatment prevented a reduction in EBC pH post-operatively, in contrast to the placebo group which demonstrated significant EBC acidification (**Figure 2**). This was associated with a significant reduction in plasma monocyte chemotactic protein-1 and urine ACR on Day 3 post-operatively and plasma RAGE on Day 7 post-operatively in the simvastatin group. No serious adverse reactions occurred.

Effects of KGF in inhaled LPS model of ALI

A randomised double blind allocation concealed placebo controlled trial (ISRCTN21056528) was conducted investigating the effects of placebo and KGF 60 mcg/kg for three days prior to LPS inhalation.

In this study, we have shown that KGF attenuates the fall in SP-D secondary to LPS inhalation. Furthermore more we have shown KGF increases granulocyte-macrophage colony-stimulating factor, which is known to increase macrophage apoptosis. In *in vitro* studies we have demonstrated that KGF promotes epithelial repair as well as increasing apoptosis of necrotic epithelial cells.

Future direction

The results of my research on the effects of simvastatin and KGF have informed the design of a multi-centre clinical trial (HARP-2) and an ongoing single centre randomised clinical trial on KGF in ALI respectively. A multi-centre trial to study the effects of simvastatin in preventing ALI

after oesophagectomy is planned based on the evidence generated from my research. This study will be powered to detect clinical outcomes including ALI.

Research papers and editorial

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Research Free Paper Presentations Joint Winner

Hospital-acquired H1N1 infection during 2010-2011 pandemic; a single centre experience

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Patients or visitors to hospital with pandemic flu virus [A(H1N1)] in a virus shedding stage can "spread" influenza to other patients resulting in nosocomial infection. This is a recognised problem in hospitals especially in the care of "at risk" populations such as children, patients with chronic diseases and the immunocompromised.[1] A study was performed to assess the prevalence and characteristics of hospital transmission of A(H1N1).

Following ethical approval a retrospective cohort study was performed. The study included all patients admitted to a tertiary referral hospital between November 2011 and January 2011 who had a positive A(H1N1) PCR and were symptomatic. Hospital-acquired A(H1N1) [HA-A(H1N1)] was defined as a positive PCR with symptoms, after admission to the hospital with an unrelated illness and after the incubation period of five days.[2]

During the last winter wave of pandemic influenza, 86 patients admitted to the referral hospital had a positive PCR for A(H1N1). In this cohort, 19 patients (22%), required treatment on an intensive care unit [ICU]. Ten (11.6%) of the 86 patients met the criteria for HA-A(H1N1). Of these patients five (50%) acquired the infection whilst admitted to an ICU, five (50%) were immunocompromised and seven (70%) developed the infection after more than seven days admitted to hospital. Eight (80%) of the cases of HA-A(H1N1) had not received vaccination against A(H1N1).

Significant transmission of A(H1N1) was found to occur within a tertiary hospital setting despite infection control measures (eg barrier nursing). Patient groups vulnerable to HA-A(H1N1) include those on ICUs, the immunocompromised and those with a protracted hospital stay. High-risk patients may benefit from an in-hospital vaccination programme to reduce nosocomial transmission. There are limitations of in-hospital vaccination, including that a two-week period may be required before protective A(H1N1) antibodies are induced.[2] However, the high burden of care necessary for A(H1N1) patients and high number of cases of HA-A(H1N1) after protracted stays in hospital may justify a vaccination programme. Further studies are required to determine the effectiveness of a vaccination programme in preventing HA-A(H1N1).

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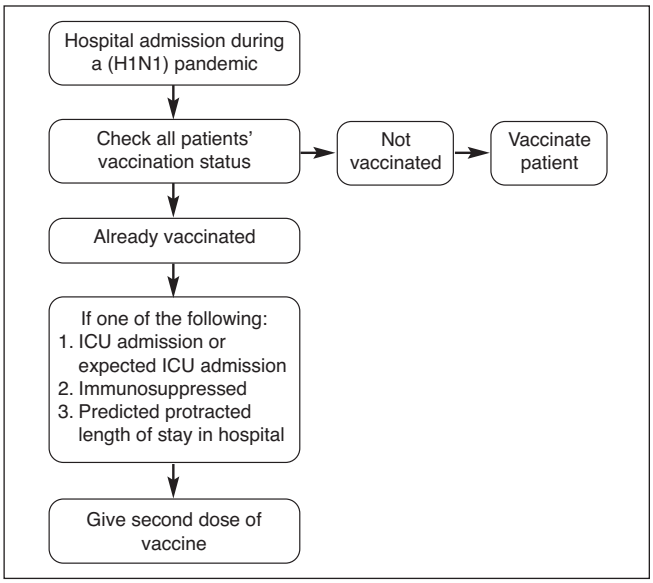

Figure 1. An approach to hospital admission during pandemic flu.

Research Free Paper Presentations Joint Winner

Simvastatin reduces systemic vascular endothelial activation/injury in acute lung injury (ALI)

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There is no effective pharmacological treatment for ALI. A recent phase 2 study in patients with ALI found simvastatin improved pulmonary and non-pulmonary organ dysfunction with a reduction in alveolar and systemic inflammation.[1] As statins also improve endothelial function this might be a further potential mechanism for the improvement in organ function in ALI. The aim of this study was to determine if vascular endothelial function was modified in this patient cohort.

The HARP study was a phase 2, double blind randomised placebo controlled trial of simvastatin 80 mg or placebo daily for up to 14 days in patients with ALI. Plasma was collected at baseline and at day 7. Von Willebrand Factor (vWF) antigen and soluble endothelial adhesion molecules, biomarkers of endothelial activation/injury, were measured. vWF was assayed by an immunoturbidometric method (Diagnostica Stago, Asnières, France). Levels of soluble intercellular adhesion molecule (sICAM)-1 and vascular cell adhesion molecule (sVCAM)-1 were measured using a Fluorokine® MAP multiplex kit (R&D Systems, Minneapolis, MN, USA). Data are presented as median (IQR) or mean (SD).

Thirty patients were randomised to simvastatin and 30 to placebo. Both

groups were well matched for baseline demographics. Baseline levels of endothelial markers were similar. Plasma vWF was lower in the simvastatin treated group compared to placebo at day 7 (183(141,285)% *vs* 252(234,463)%, p=0.03, **Figure 1**). The level of sVCAM-1 was also lower in the simvastatin group at day 7 (1872(538) ng/mL *vs* 1469(405) ng/mL, p=0.02, **Figure 2**).

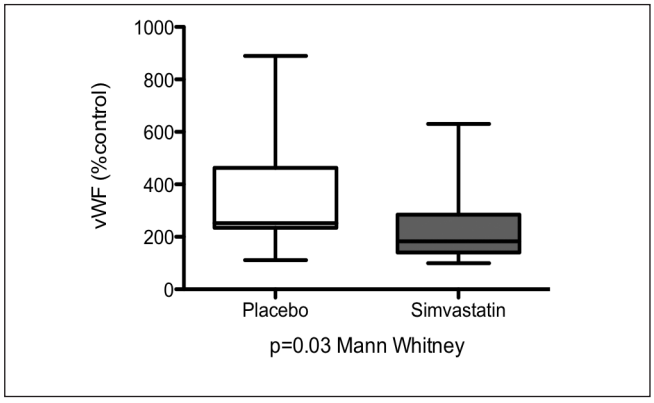

Figure 1. Plasma vWF significantly lower in simvastatin treated patients at day 7.

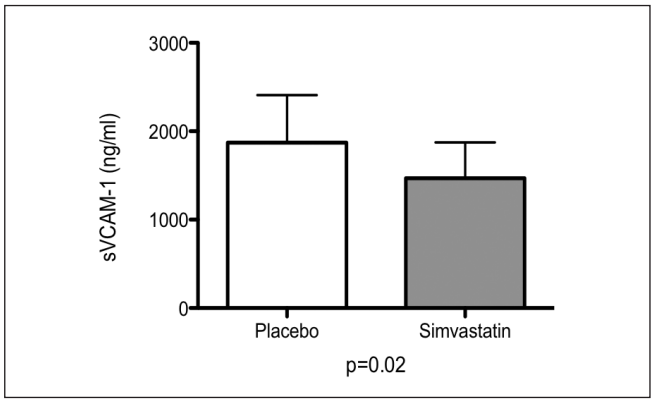

Figure 2. sVCAM is significantly lower in the simvastatin treated group at day 7.

Simvastatin therapy attenuated systemic vascular endothelial activation/injury in ALI/ARDS which may be an important mechanism for the improvement in systemic organ function associated with statins in ALI. A reduction in the extra-pulmonary organ dysfunction, which is seen commonly in association with ALI, may be an important factor for potential benefit of statins in ALI. Further large clinical trials are required to confirm the significance of these findings.

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Research Free Paper Presentations

Maintenance of calcium homeostasis during citrate-based renal replacement therapy prevents parathyroid hormone secretion in critically ill patients

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Regional anticoagulation with citrate is a well established technique to maintain circuit patency during continuous renal replacement therapy (CRRT). Citrate is infused pre-filter and inhibits coagulation by chelating ionised calcium (Ca_i). Calcium (Ca) is infused before the blood returns to the patient. Citrate based CRRT is associated with longer circuit life, less bleeding complications and lower blood transfusion requirements compared to anticoagulation with heparin. Previous studies in patients with acute kidney injury (AKI) treated with citrate-based CRRT reported negative daily calcium balance and significant parathyroid hormone (PTH) release within 48 hr when using protocols aiming for serum Ca_i between 0.8-1.1 mmol/L.[1] Concern was raised about potential negative effects on bone metabolism.[1,2]

The aim of our study was to assess whether a citrate protocol aiming for systemic Ca_i levels in the physiologic range (1.12-1.20 mmol/L) could prevent PTH release. The primary outcome was variation in serial PTH levels whilst on CRRT for a 48h period. Univariate analysis was performed to investigate differences across all time points. A random effects model was used to investigate time trends in PTH levels and the association between PTH and Ca_i.

Thirty consecutive critically ill patients [mean age: 70.4 (11.3) years; 56.7% males] with AKI receiving citrate-based CRRT were prospectively evaluated in a single-center observational study.

	Baseline	12 hr	24 hr	48 hr	p-value
Number of patients with PTH result	30	28	25	22	
PTH [pg/mL] median (IQR)	66.5 (43-111)	109 (59.5-151.5)	88 (47-124)	85 (53-133)	0.532
Ca_i, [mmol/L] mean (SD)	1.15 (0.09)	1.13 (0.09)	1.17 (0.05)	1.16 (0.04)	0.254
Number of patients with Ca_i <1.12, (%)	7 (23.3)	9 (30.0)	4 (25.4)	4 (17.4)	0.553

The differences across all time points and between baseline and 12 hours were not statistically significant (p=0.532 and p=0.164, respectively). The results were unchanged after adjustment for age, gender, magnesium levels and time spent on CRRT. In the random effects model, each 0.1 mmol/L decrease in Ca_i was associated with a 30.2% increase in PTH (p<0.001) confirming the physiologic association between serum Cai and PTH secretion.

This is the first study demonstrating that maintaining systemic Ca_i levels within the physiologic range can prevent PTH secretion during citrate-based CRRT. Whether this effect contributes to clinically relevant benefits on bone metabolism needs to be addressed in future studies.

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Use of the Medical Research Council sumscore to predict clinical outcome in critically ill patients

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Intensive care unit-acquired weakness (ICU-AW) is commonly diagnosed using manual muscle testing, in the form of the Medical Research Council sumscore (MRC-SS). Although a simple bedside test, the MRC-SS is volitional in nature and this poses limitations for its ability to distinguish poor motivation and impaired cognition from actual loss of muscle function. The aim of this study was to determine the ability of the MRC-SS to predict clinical outcome in critically ill patients.

Unselected, adult ICU patients (≥18 years) ventilated for ≥48 hours

were eligible. Conscious level of the patients was determined using the Richmond Agitation Sedation Scale; a score -one to +one was indicative of awakening. Testing comprised of a two-stage process – Stage 1, patients at awakening were required to follow four simple, one-stage commands; Stage 2, MRC-SS testing was performed by a specialist ICU rehabilitation if all four one-stage commands were successfully completed. ICU-AW was defined as MRC-SS <48. ICU and hospital mortality and length of stay (LOS) were recorded in all the patients.

Ninety-four sequential awakening patients were recruited; 68.1% males (n=64), mean age for the whole cohort of 64.5±15.3 years. Twenty-nine patients were unable to successfully complete the four one-stage commands as a result of cognitive impairment. ICU-AW was present in 73.9% of the 65 patients in whom MRC-SS testing was completed. Inability to perform the MRC-SS demonstrated a high negative predictive value for ICU mortality. Similarly a high negative predictive value was evident for ICU and hospital mortality and ICU LOS for diagnosis of ICU-AW using the MRC-SS (**Table 1**). A low positive predictive value was evident for all clinical outcomes with regard to inability to perform the MRC-SS or diagnosis of ICU-AW.

Characteristic	ICU mortality		ICU LOS (≤14; >14days)		Hospital mortality		Hospital LOS (≤28; >28 days)	
	UTC	ICU-AW	UTC	ICU-AW	UTC	ICU-AW	UTC	ICU-AW
Sensitivity	0.69	0.88	0.22	0.93	0.56	0.81	0.17	0.84
Specificity	0.84	0.28	0.64	0.41	0.84	0.29	0.56	0.41
PPV	0.62	0.15	0.28	0.54	0.69	0.27	0.28	0.67
NPV	0.88	0.94	0.57	0.88	0.75	0.82	0.42	0.65

Definitions: ICU – intensive care unit. LOS – length of stay. UTC – unable to complete four one-stage commands. ICU-AW – intensive care unit-acquired weakness. PPV – positive predictive value. NPV – negative predictive value. UTC (n=29). MRC-SS <48 (n=48). MRC-SS ≥48 (n=17).

Table 1. Characteristics of the Medical Research Council sumscore for predicting clinical outcome.

MRC-SS testing could not be performed in almost one-third of critically ill patients, from a sequential cohort, who could not complete four one-stage commands. Although inability to successfully complete the one-stage commands conferred limited predictive value, those patients that could perform this task were more likely to survive ICU. Similarly an MRC-SS <48 at awakening, presumed indicative of ICU-AW, conferred limited predictive value. However an MRC-SS ≥48 predicted ICU and hospital survival as well as an ICU LOS less than two weeks. These data highlight the limitations of volitional tests in critically ill patients and clearly challenge the current view that ICU-AW, as measured by volitional tests, predicts poor outcome. These data confirm that preserved peripheral strength predicts a good outcome.

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The authors declare no conflict of interests.

A randomised trial comparing restrictive with liberal transfusion strategies for older critically ill patients requiring prolonged mechanical ventilation

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Restricting blood transfusions appears safe for most critically ill patients,[1] but clinical uncertainty exists for older sicker patients, especially those with cardio-respiratory co-morbidities.

We carried out a parallel group randomised feasibility trial with patient blinding to group allocation in six UK ICUs between August 2009 and December 2010. Entry criteria were: age ≥55 years; a requirement for ≥96 hours mechanical ventilation; haemoglobin (Hb) concentration ≤90 g/L; and expectation of ≥24 hours of further mechanical ventilation at the time of randomisation. Exclusion criteria included: active bleeding at the time of screening; traumatic brain injury; intracranial haemorrhage; and patients not expected to survive >48 hours. Randomisation was 1:1 to two transfusion strategy groups, with allocation concealment. Minimisation by centre and the presence of ischaemic heart disease, including a random element, was used. The restrictive group was transfused with a Hb trigger of ≤70 g/L, and target Hb 71-90 g/L; the liberal group with a Hb trigger of ≤90 g/L, and target 91-110 g/L. The intervention period lasted 14 days or the remainder of ICU stay, whichever was longest. The main feasibility outcome was the difference in Hb. Secondary outcomes included organ failure progression in the ICU, and mortality, disability (Rivermead Mobility Index), quality of life (HRQoL; SF-12) and healthcare costs over 180 days follow up.

A pre-planned sample size of 100 patients was randomised (51 restrictive; 49 liberal groups). Patients were well-balanced at baseline and had a high prevalence of pre-existing co-morbidities and organ failures. Mean Hb during the intervention period for restrictive and liberal groups was 81.9 (SD 5.1) and 95.7 (6.3) g/L respectively (difference 13.8 g/L (95% CI: 11.5 to 16.0); p<0.0001). This difference persisted until hospital discharge. 21.6% fewer patients in the restrictive group were transfused post-randomisation (p<0.001) and red cell blood (RBC) use was 15% lower in the restrictive group (median difference in RBC use 1 unit (95% CI: 1 to 2; p=0.002). Protocol compliance was excellent. There were no major differences in organ failure progression but confidence intervals were wide. A trend towards improved survival over 180 days with the restrictive strategy was observed (mortality 37.3% *vs* 55.1%; Hazard Ratio 0.60 (95% CI: 0.34 to 1.09; p=0.089)). Physical function and HRQoL were generally poor among survivors. Healthcare costs were higher for patients managed with the restrictive strategy (mean difference £18,265 (95% CI, -1310 to 37,841) largely as a result of greater survival.

In conclusion, despite high illness severity the observed treatment effect in this feasibility trial favoured the restrictive transfusion practice.

Trial Registration: Clinicaltrials.gov NCT00944112; Funder: Chief Scientists Office, Scotland

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Scottish intensive care and mortality – shedding light on out-of-hours admissions

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Critically ill patients can present to the intensive care unit (ICU) at any time of day despite variations in staffing levels, treatment and diagnostic resources. Several cohort studies have considered the impact of admission time on patient outcome with conflicting results.[1-3] We investigated whether ICU admission time affects mortality and hospital stay.

A retrospective cohort analysis of adult ICU admissions within Greater Glasgow and Clyde NHS Health Board from January 2007 to 2011 was performed. Demographic (age, sex), admission (specialty, time, APACHE II) and outcome data (ICU/hospital mortality and stay) were extracted from the Scottish Intensive Care Society Audit Database. Admission time was categorised into day (07:45-19:45), night (19:45-07:45) and weekend (19:45 Friday-07:45 Monday). Univariate analyses of quantitative and qualitative variables with mortality were performed using Mann-Whitney or Kruskal-Wallis and chi-squared tests respectively according to Anderson-Darling test for normality. Variables univariately associated with mortality

entered a logistic regression analysis to identify independent risk factors. All analyses performed using Minitab 16 at a significance level of 5%.

In total, 7912 patients (57(17)yr, APACHE II 17(11-23[0-53])) were admitted to ICU during this period (day 3091 (39.1%), night 2314 (29.2%), weekend 2507 (31.7%)). ICU mortality (day 598 (19.3%), night 491 (21.2%), weekend 566 (22.6%)) was significantly associated with age (p<0.001), APACHE II (p<0.001) and admitting specialty (p<0.001). Weekend admissions had significantly higher adjusted ICU mortality (odds ratio (OR),1.26[95%CI 1.10, 1.45]; p=0.001) but not night (OR,1.13[95%CI 0.98, 1.3]; p=0.089). Hospital stay of survivors admitted during the day was significantly longer than out of hours (night and weekend) admissions (14(6-28[0-341]) *vs* 12(5-27[0-341]), p=0.001).

Patients admitted during the weekend to ICU in the west of Scotland have an increased risk of death compared to those admitted through the week. Similarities in age and acute physiology severity scores across all time periods implicates other patient, organisational, physician or nurse related factors.

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Clinical Practice Free Paper Presentations winner

A prospective multicentre observational study of iatrogenic events preceeding intensive care unit admission (PREVENT)

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Published data from North America and France show that 3.7 to 19.5% of admissions to intensive care units (ICU) are associated with iatrogenic events.[1] None of the studies have been performed in the NHS, and only one of the studies published is multi centre.[2] Hence we undertook a comprehensive review to ascertain the incidence, type, severity and preventability of iatrogenic events leading to ICU admission in six UK hospitals.

Following ethical approval all adult emergency admissions to six UK ICUs (Royal Berkshire, John Radcliffe, Wexham Park, Stoke Mandeville, Milton Keynes and Lewisham Hospital) were prospectively audited over a continuous six-week period. Patients' case notes were reviewed on admission to the ICU by physicians who had been trained according to a strict protocol. A proforma was used to guide the investigators through the notes in a proscriptive manner to ensure sensitivity and consistency in data collection. An iatrogenic event was defined as occurring as a result of improper action or inaction. The notes were reviewed again on discharge, all events being reviewed by two separate investigators.

Preliminary analysis of the data shows that during the study period 129 out of 329 ICU admissions were due to an iatrogenic event (39%). Patient demographics and class of ICU admission were similar between the two groups.

A total of 195 events were recorded; 40(22%) were drug events, 22(12%) were surgical events, nine (5%) were anaesthetic events, 15 (8%) were procedure events, 23 (13%) were nursing events, 76 (42%) were medical management events, two (1%) were equipment events and 11 (6%) were infective events. The severity of events was also recorded (**Figure 1**). There was no statistically significant difference between the length of stay of stay on ICU or the number of organs supported.

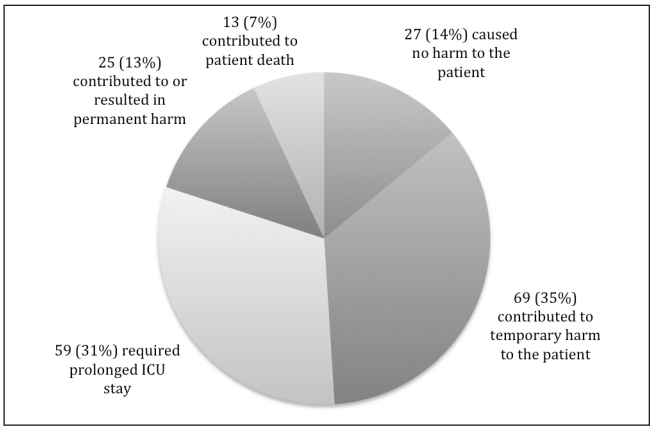

Figure 1. Severity of iatrogenic events.

To our knowledge this is the first report of iatrogenic events associated with ICU admission in the NHS. We found a higher event rate when compared with previously published data. Thirty nine percent of admissions were associated with one or more events, with 20% of the events resulting in permanent harm or death.

There are no conflicts of interest.

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Clinical Practice Free Paper Presentations

Quality improvement on the ICU through the clinical microsystems approach: the SLAVED process check

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Healthcare organisations display poor levels of reliability[1] when delivering routine interventions. Intensive care medicine is underpinned by multiple examples of daily routine processes that are demonstrated to improve patient outcomes.

Our intensive care unit (ICU) has developed a quality improvement (QI) initiative based on a lead multidisciplinary group. Using the Clinical Microsystems (CMS)[2] approach to QI our group identified daily elements of care with a strong evidence base and developed an embedded process (the SLAVED check) to ensure high levels of reliability in their delivery on our ICU. SLAVED is an acronym constructed from individual interventions. Junior medical and nursing staff separately perform daily assessments, including consideration of SLAVED elements. Subsequent discussion between the groups results in setting of SLAVED goals. We used a Plan-Do-Study-Act (PDSA) approach to implement the SLAVED process. During PDSA cycles we collected data on the number of SLAVED goals set and achieved for each element in all patients resident on our ICU during week-long periods.

Baseline data collected showed poor reliability; individual process elements were addressed in a mean 25% of patients. Introduction of the SLAVED process check increased reliability levels to a minimum of 80% of goals set in all patients. We subsequently introduced a reminder step; clerical staff check computerised documentation to ensure SLAVED is completed. If a SLAVED check is not documented a reminder is sent to the responsible medical staff; this increased reliability levels to 90%. Our final PDSA cycle introduced consultant checking of set goals; if the goal is considered inappropriate it is altered. Following this we now achieve appropriate goals in a mean of 97.5% of process elements.

The use a standardised checklist is typically associated with a reliability

level of between 80 and 90%. The introduction of additional "error proofing" strategies including multidisiplinary ownership, a clerical check and consultant review has improved the reliability of the process to the next level (described as 95%).[1]

The use of quality improvement methodology to introduce the SLAVED process check has resulted in a stable level of compliance in the delivery of evidence based small-scale interventions on our ICU. The process check provides a safety net to ensure that all elements are completed on all patients ("every patient, every day"), mitigating the aspect of human error that exists in delivery of health care. The underlying QI processes can be transferred to other patient interventions associated with ICU.

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Ultrasound equipment disinfection practice in the ICU setting; results of an educational intervention to improve disinfection practice and mitigate risk of cross-infection

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Following two concomitant MRSA bacteraemias in the intensive care unit (ICU) a root cause analysis highlighted ultrasound (US) equipment as a potential vector of cross-infection. It has been shown that 7% of randomly-sampled US machines are contaminated with potential pathogens,[1] and that bacterial growth occurs in US transmission-coupling gel.[2] Consequently an audit was planned to assess US disinfection practice and to intervene as necessary to mitigate the risk of cross-infection.

Best-practice standards[1] were defined following a MEDLINE search as: Before and after every use of US equipment:

1. Disinfect hands.
2. Clean US machine with disinfectant wipes.
3. Clean US probe with disinfectant spray.

In addition, when near any break in the skin a sterile plastic probe cover and sterile US gel should be used.

An initial observational audit carried out on an *ad hoc* opportunistic basis compared actual practice to best-practice. Disinfection practice was recorded for all types of US usage. A mini-poster intervention was created depicting the guidelines and then displayed on the US machines. Images of blood agar plates cultured from optimally-disinfected and non-disinfected US probes (showing no growth and heavy growth respectively) were incorporated to highlight the efficacy and importance of the disinfection protocol.

Audit cycle (number of observations)	1 (n=34)	2 (n=21)	3 (n=17)
Disinfection attempted before use (n %)	15 (44)	15 (71)	17 (100)
Optimal disinfection* before use (n %)	2 (6)	12 (57)	14 (82)
Disinfection attempted after use (n %)	22 (65)	20 (95)	15 (88)
Optimal disinfection* after use (n %)	3 (9)	17 (81)	13 (76)
Sterile probe cover and sterile US gel used near a break in the skin (n %)	29 (85)	19 (90)	15 (88)
Hand hygiene before and after use (n %)	34 (100)	21 (100)	17 (100)

*US machine cleaned with disinfectant wipes and US probe cleaned with disinfectant spray

Following re-audit, disinfection practice was found to have improved. Remaining disparities were addressed by enhancing the mini-poster to make it more visually-striking and by simplifying the guidelines into four key steps with illustrative photographs. An educational presentation raising awareness was given to ICU staff and subsequently a final audit was carried out.

Our final interventions led to large improvements in the quality of US disinfection, including an increased incidence of optimal disinfection before use from 6% to 82% and of optimal disinfection after use from 9% to 76% (table). Our poster and educational presentation addressed common knowledge-gaps among doctors. In particular there was some unawareness that sterile plastic probe covers are not impervious to bacterial translocation and that probes therefore require disinfection before their use. We learnt that for interventions to have the highest impact they need to be 'eye-catching' and that guidelines must be simple and succinct to be appreciated during busy clinical practice. With disinfection practice improving significantly before and after use of US, this minimal-cost intervention goes a long way to mitigating risk of cross-infections and therefore would be useful in all ITUs. Improving compliance further in future will require novel interventions to reinforce and raise awareness. To disseminate this knowledge and practice widely it should be added to local policies and mandatory trust and departmental induction schemes.

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Effect of the introduction of a primary PCI service on out-of-hospital cardiac arrest outcomes across a city

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Primary percutaneous coronary intervention (PCI) has been recommended in the treatment of out-of-hospital cardiac arrest (OHCA). Bristol has two hospitals with emergency departments. In 2008 a primary PCI service was started in one hospital. Our aim was to determine the effects of this on hospital mortality and ICU admission patterns across the city.

	SMR *vs* ICNARC prediction (95% CI)	Absolute risk reduction for mortality *vs* all OHCA (95% CI)	Number needed to treat to prevent one death (95% CI)
All patients who received angiography	0.70 (0.49- 0.98)	0.23 (0.09-0.37)	4 (3-11)
Patients who had angiography and PCI	0.65 (0.38-1.05)	0.25 (0.07-0.42)	4 (2-13)
Patients who had angiography but no PCI	0.85 (0.49-1.38)	0.13 (-0.05 - 0.32)	8 (-3 - 22)

A retrospective case review was performed of all ICU admissions for OHCA during a period three years before and two years after the introduction of the primary PCI service. Data were collected on hospital discharge status of patients, and whether angiography or PCI were performed. The primary outcome measure was survival to hospital discharge. Patients with incomplete notes were excluded.

The total admissions in Bristol increased from 114 (38 admissions/year) to 121 (60.5/year). They increased in the PCI centre from 74 (24.6/year) to 98 (49/year) but decreased in the non-PCI centre from 40 (13.3/year) to 23 (11.5/year).

The overall Standardised Mortality Ratio (SMR) *vs* ICNARC prediction was 0.95 (95% CI 0.73-1.18) in the first period and 0.89 (CI 0.71-1.12, NS) in the second. There was also no significant change in the SMR between the two periods in either individual hospital. Forty-nine percent of patients admitted during the second period received angiography.

Overall, patients who received PCI had a trend towards increased

survival, without evidence of worsened outcome in patients who undergo the risks of angiography without intervention. Our study has not demonstrated a statistically significant improvement in mortality in OHCA associated with the establishment of a primary PCI service. We estimate that for adequate power to demonstrate improved mortality, a trial comparing a group with availability of primary PCI with a group without would need 320 patients in each arm.

This study has demonstrated that since establishment of a primary PCI service, the number of admissions with OHCA to the ICU with the PCI service has almost doubled, with a proportional fall in admission rate at the other unit. This may have significant workload implications. Further work should investigate changes in length of stay and implications for care of other ICU patients.

Use of an extracorporeal lung assist device as rescue therapy to minimise ventilator-associated lung injury in patients with severe ARDS: a series of thirteen cases from a district hospital

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Acute respiratory distress syndrome remains a cause of significant morbidity and mortality in the ICU population. Management is supportive however it is well recognised that mechanical ventilation contributes to lung injury.[1] Small subgroups of patients with ARDS have such poor lung compliance that conventional ventilation proves ineffective.

The Novalung® is an extracorporeal lung assist device used to support respiratory function in patients with predominantly hypercapnic respiratory failure. It has been used successfully in our unit as rescue therapy in patients with severe ARDS.

A retrospective case note analysis was performed on all patients who had received Novalung therapy. Respiratory, cardiovascular and arterial blood gas biochemistry were recorded prior to initiation of Novalung therapy and at four, 24 hours and at the end of treatment, along with patient demographics. Outcome data recorded included survival to ICU and hospital discharge. Any complications were reported.

Parameter	Before commencement	4 hr post commencement	P value
$PaCO_2$ (kPa)	12.83 (2.33)	8.15 (1.84)	<0.0001
pH	7.09 (0.09)	7.30 (0.08)	<0.0001
PPeak (cmH_2O)	30.8 (5.1)	26.1(4.4)	<0.001
Vt (mL/kg)	5.23 (0.89)	3.72 (1.42)	<0.001
PaO_2/FiO_2 ratio	16.5 (6.4)	16.3(7.4)	NS
Noradrenaline dose (μg/kg/min)	0.17(0.17)	0.17(0.19)	NS
Values are means (SD)			

Table 1: Results

In 54 months, 13 patients were treated with the Novalung. All had severe ARDS with sepsis being the most common causative factor. Following commencement of therapy, significant improvements in arterial blood gas values and ventilatory mechanics were seen (**Table 1**, previous page). One patient suffered a minor vascular complication. Nine (69%) patients survived to discharge from ICU.

There is a large and growing body of evidence describing the harm caused by mechanical ventilation in patients with diseased and poorly compliant lungs. It has been suggested that 'ultra-low tidal volume ventilation' may confer benefit by further limiting ventilator associated lung injury. The use of the Novalung device for rescue therapy in severe ARDS facilitated low tidal volume ventilation. We have found that this device can be used safely and effectively in a district hospital setting.

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Iatrogenic blood loss in the critically ill: a re-audit of blood testing in a teaching hospital intensive care unit

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Anaemia occurs commonly in the patients admitted to the intensive care unit (ICU). It is in part contributed by frequent blood sampling. A previous audit performed in our hospital showed that the average volume of blood taken from each patient per day was higher than the number recorded from the ABC study,[1] and this could have significant impact on the haemoglobin levels in our patients.[2] The aim of this re-audit is to assess the current practice in frequency of phlebotomy and the volume of blood loss after implementing the changes that the original audit suggested.

This retrospective audit was undertaken in a 13-bed ICU. Over a two-week period, all blood samples ordered for each patient were recorded from the hospital computer system. The volume required for each bottle was discovered from the product literature. The blood volume taken was then calculated, and this volume included the 2 mL of discarded blood for clearing the 'dead space' of the arterial line before each set of samples was obtained (3 mL was discarded in the baseline audit). As recommended in the original audit, the 3 mL arterial blood gas (ABG) syringes were changed to 1 mL ones. Where a bed space was only occupied for part of a 24-hour period, the entire 24-hour period (patient-day) was excluded from the study.

One hundred and forty-six patient-days were included in the study. The total volume taken was 6253.6 mL (7910 mL in the original study which included 151 patient-days), and this gives an average of 42.8 mL (13.7-164.6 mL) per patient-day (18.3% reduction comparing with 52.4 mL (0-128.7 mL) in previous study, p<0.001). The most frequently performed test was ABG analysis, and as before, we were still taking on average of 5.8 times (0-17) per patient-day. However, after changing our practice, the average volume of blood taken from ABG analysis alone reduced from 29 mL (in previous study) to 11.5 mL (60% reduction, p<0.001).

This re-audit has demonstrated a significant reduction in the volume of blood loss in ICU patients after introducing the smaller ABG syringes and discarding less blood. This could potentially reduce the incidence of iatrogenic anaemia and even blood transfusion rate in these patients. This study highlights the importance of small changes to the practice could have a significant impact on patient outcome on ICU. It also encourages both medical and nursing staff to consider different ways of reducing iatrogenic blood loss, for example, by reducing frequency of phlebotomy or returning the wasted 'dead space' blood back to the patients.

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The prognostic value of sequential organ failure assessment (SOFA) scores ("delta-SOFA") in critically ill patients with haematological malignancies

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Patients with haematological malignancy are frequently perceived to have poor outcomes. This study investigated prognostic indictors and outcomes in adult patients with haematological malignancy admitted to an intensive

care unit (ICU) over a one-year period.

All consecutive adult ICU admissions with haematological malignancy from the beginning of October 2009 to the end of September 2010 were extracted from electronic patient records (IntelliVue Clinical Information Portfolio (ICIP), Phillips Medical Systems). A manual search of the unit's admissions book was also performed to identify eligible patients for inclusion. Data collection was performed retrospectively from ICIP. Data collected included patient demographics, APACHE II score, haematological diagnosis, platelet and neutrophil count and requirements for organ support. SOFA scores were calculated on admission and at 24, 48, 72 and 96 hours following admission. Delta-SOFA ($_{x}$SOFA = (SOFA at x – SOFA at x-24 hours) scores were subsequently calculated. ICU, hospital and three month mortality was collected.

Thirty-six admissions of 30 patients were identified during the study period. The most frequent haematological diagnoses were lymphoma, 10(32%) and chronic lymphocytic leukaemia, seven (23%). Ten (32%) patients had received a bone marrow transplant. The mean age was 58 years and the median APACHE II score was 24(Interquartile range 20-34). Sepsis was the leading cause of ICU admission 27 (71%), six (19%) of which were related to indwelling vascular devices. Sixteen (60%) of the admissions involved two or more organ system failures. ICU, hospital and three-month mortality was 13 (36%), 16 (53%) and 19 (63%) respectively. APACHE II scores were predictive of outcome. An APACHE II score of >30 was associated with an ICU mortality of seven (70%) and a overall three month mortality of eight (80)%. An increase of delta-SOFA score by >five from admission to 24 hours was indicative of 100% ICU mortality.

The ICU and hospital mortality of patients with haematology malignancy in our study appear similar to recently published data from Scottish ICUs.[1] This reinforces the view that outcomes in this cohort are similar to those in non-cancer patients with multiple organ failure and better than historical (nihilistic) perceptions. It has been proposed that serial evaluation of SOFA scores ("delta-SOFA") can predict outcome in a heterogeneous population of critically ill patients.[2] Although this study was limited by size, our data did replicate this for critically ill patients with haematological malignancies.

This study merits further prospective work to identify prognostic factors associated with mortality in patients with haematological malignancies.

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Airway management training, a multi-modalities approach to meet an identified training need

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On our intensive care unit (ICU) senior medical and nursing staff had identified the need for specific airway training based on analysis of local incidents and near misses, this was strengthened by specific recommendations of the Royal College of Anaesthetists National Audit Program 4. In response to this we developed a training programme for the nursing staff combining multiple teaching modalities, including *in situ* simulation. Simulation training has been shown to both be effective in teaching technical and non-technical skills (such as good team working)[1] and is perceived as educational and enjoyable by the participants.[2]

The four-hour training session comprised:

- A lecture covering basic airway anatomy and assessment, intubation drill and difficult airway equipment.
- A skill-station covering basic airway manoeuvres and adjuncts, based upon the Adult Life Support airway station.[3]
- *In situ* simulation comprising of a scenario to highlight the importance of a multi-disciplinary team approach to managing intubation on the ICU.
- A formal review and familiarisation of the contents on the difficult airway trolley, including discussion of the appropriate use of the different devices in a 'Can't Intubate, Can't Ventilate' situation.

Simulation was integral to the day, as it offered the opportunity for staff (who in many cases had no previous formal airway training) to safely practise the management of airway emergencies in a familiar environment, using the equipment that would be available in a real emergency. We asked all participants to fill in a questionnaire before the course to assess their expectations and previous experience; and afterwards to provide detailed feedback. This consisted of eight questions graded using a seven point Likert-type scale and four questions for free-text feedback of particular strengths and weaknesses of the training.

Eighty-nine nurses were trained, of various grades over seven sessions, 25% of whom felt they had had inadequate training previously and 94% of whom had a desire to learn new skills. The feedback was excellent with 97% of participants feeling more confident in their skills, 98% feeling they had learned new skills from the sessions and 98% declaring the training was relevant to their needs. There was a positive (though non-significant) correlation between having adequate pre-course training and all positive post-course feedback points suggesting that the course had value for even those that felt adequately trained.

We have found that a training day including *in situ* simulation had been effective in improving the confidence of our nursing staff in their abilities to deal with future airway emergencies. Even among those that rated their confidence as already being high there was a great appetite for this programme, most likely as intubation is seen as a high risk intervention. Due to the positive feedback received we will be delivering this training to the ICU nursing staff across all the hospitals in our Trust.

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Comparison of creatinine clearance with equations estimating glomerular filtration rate in the intensive care unit

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In intensive care units (ICU), estimating glomerular filtration rate (GFR) is important for adjusting drug doses and monitoring renal function. Serum creatinine based equations are commonly used but have not been validated in the ICU setting. Clearance based methods are more accurate for estimating GFR in certain situations.[1] We assessed the degree of agreement between 24-hour creatinine clearance (CrCl) and estimated GFR (eGRF) based on two equations: Modification of Diet in Renal Disease equation (MDRD) and Chronic Kidney Disease–Epidemiology Collaboration equation (CKD-EPI) in the ICU environment.

Data was collected retrospectively for patients with eGFR (MDRD or CKD-EPI) <90 mL/min/1.73^2 who had also had a corresponding CrCl measured. Bland-Altman and Kappa analysis were used to measure the strength of agreement between CrCl and the two equations. Kappa between 0.21-0.40 is considered fair agreement, 0.41-0.6 moderate, 0.61-0.8 substantial and 0.81-1.00 near perfect agreement. Concordance between the equations and CrCl for classification into one of the drug dosing categories: CrCl <20 mL/min, 20-35 mL/min, 36-59 mL/min and >60 mL/min was also determined.

We analysed 397 MDRD results and 396 CKD-EPI results. Using Bland-Altman analysis, bias for MDRD was -4.6 (95%CI, -47 to 37) while for CKD-EPI was -7.1 (95%CI, -53 to 39). Kappa for MDRD was 0.69 (95%CI, 0.62-0.76) and for CKD-EPI was 0.66 (95%CI, 0.58-0.73). **Table 1** represents concordance between CrCl and both equations.

	MDRD equation			CKD-EPI equation		
CrCl (mL/min)	Concordant(%)	Discordant(%)		Concordant(%)	Discordant(%)	
		<CrCl	>CrCl		<CrCl	>CrCl
<20	46	–	64	46	–	64
20-35	29	6	65	27	7	66
36-59	50	8	42	42	8	50
>60	81	19	–	81	19	–

Table 1. Concordance and discordance between eGFR and creatinine clearance according to drug dosing category.

Although the bias is small and kappa shows substantial agreement between the equations and CrCl, the confidence intervals for the bias are so far apart that neither equation should be used in place of CrCl in the ICU setting. In addition, the concordance of eGFR values when CrCl <60 mL/min is poor. Two thirds of patients in the lower CrCl categories will be wrongly assigned to a higher CrCl drug dosing category when the equations are used in place of CrCl. This could have serious implications if the wrong drug dose is administered.

Therefore, the CKD EPI and MDRD equations should not be used interchangeably with CrCr in ITU patients with impaired renal function.

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International Sepsis Forum Research Poster winner

Deactivated monocytes: not hypo-responsive but reprogrammed?

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Monocyte deactivation has been described in the context of critical illness and is characterised by reduced inflammatory cytokine production together with reduced HLA-DR expression and impaired antigen presentation.[1] Tumour necrosis factor-α (TNF) converting enzyme (TACE) is expressed on monocytes[2] and is responsible for the shedding of membrane proteins, including soluble (sol)-TNF and the adhesion molecule L-selectin. We sought to determine whether TACE activity and substrate shedding in critically ill patients would be altered when compared to healthy controls.

Blood samples (day 0, 2, 4 and 6) were taken from mechanically ventilated patients (n=5) who had the systemic inflammatory response syndrome (SIRS). Purified blood monocytes were obtained by magnetic CD14 positive bead selection from peripheral blood mononuclear cells (PBMCs). Monocytes were washed and exposed to a LPS stimulus (1µg/mL for 60 minutes) before having their TACE activity quantified using a cell-based fluorometric catalytic activity assay.[3,4] Monocyte expression levels of HLA-DR and of pre and post-LPS TACE and L-selectin were determined via flow cytometry. PBMC's were also placed in 16-hour LPS culture and had sol-TNF production quantified by ELISA.

Monocytes from the SIRS patients displayed reduced HLA-DR levels and sol-TNF production when compared to healthy controls consistent with deactivation. TACE expression levels were not altered by SIRS. Basal TACE activity in the SIRS patients' monocytes increased over time compared to controls (**Figure 1a**). In controls LPS produced TACE activity up-regulation whereas in SIRS this was substantially attenuated (**Figure 1b**). In contrast, LPS-induced L-selectin shedding was not altered in SIRS.

These results suggest that the systemic inflammatory response does not produce a globally hypo-responsive/anergic state in monocytes. Cells may be reprogrammed or have altered regulation in specific pathways but appear to retain the ability to shed L-selectin. This may act to prevent leukocyte aggregation in non-inflamed tissues and therefore be in keeping with a phenotype that acts to prevent widespread dissemination of inflammation. Further work is needed to examine these effects in more homogeneous patient groups. However, our results suggest that the term 'monocyte reprogramming' may be more appropriate than 'monocyte deactivation' to represent changes in monocyte inflammatory response during SIRS.

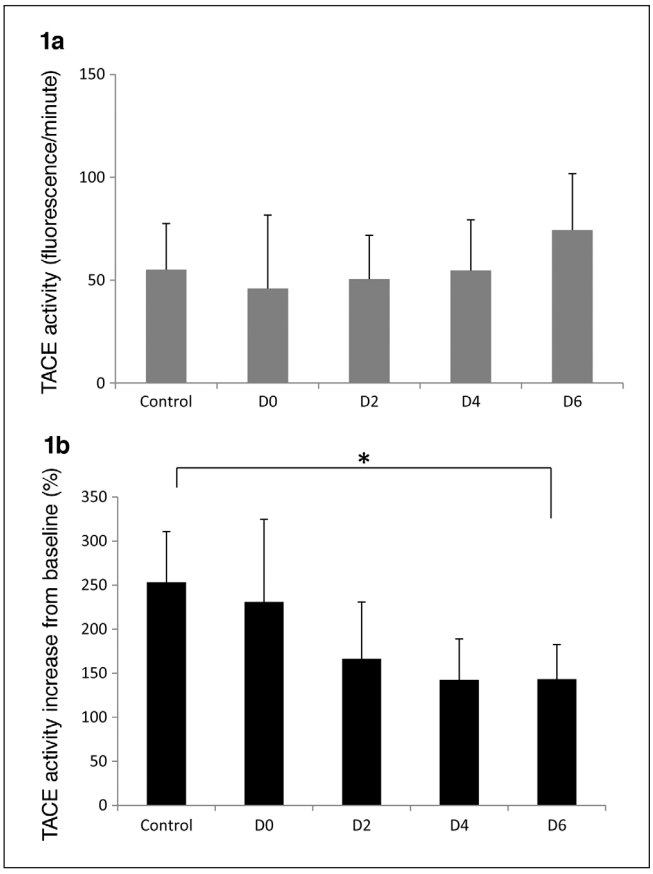

Figure 1a and 1b. TACE activity changes over sampling time course (mean + SD), n=3-5. (a): Baseline (un-stimulated) activity levels. (b) Activity increase from baseline (%) on LPS exposure. * p<0.05 ANOVA with Bonferroni correction.

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British Thoracic Society Care Group Free Paper joint winner

Sialic acid conjugated poly(lactic-co-glycolic) acid nanoparticles target Siglec receptors and elicit potent anti-inflammatory effects; a potential novel therapy for ALI

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Acute lung injury (ALI) is characterised by the uncontrolled activation of

immune cells, resulting in dysregulated inflammation that results in injury to the alveolar epithelium and endothelium. Sialic acid-binding Ig-like lectins (Siglecs) are cell-surface inhibitory receptors found predominantly on myeloid cells. Siglec cross-linking inhibits pro-inflammatory signalling in these cells and consequently, the targeted ligation of Siglecs represents an attractive therapeutic strategy in ALI and sepsis. The aim of this study was to investigate the anti-inflammatory effects of di-sialic acid coated nanoparticles.

We prepared poly(lactic-co-glycolic acid) (PLGA) nanoparticles with di(α2-8) N-acetylneuraminic acid (NANA) conjugated on the surface. We then examined the ability of these particles to elicit anti-inflammatory effects *in vitro* on murine and human macrophages and *in vivo* in a murine LPS model.

We found that these particles bound macrophages through cell surface Siglec receptors and caused a significant reduction in LPS-induced IL-6 and TNFα *in vitro* (**Figure 1a**). Mortality was prevented by the nanoparticles in the murine LPS model; even when treatment was given 2 hr post LPS after the inflammatory process was established (**Figure 1b**).

These results clearly show these di-sialic acid-conjugated nanoparticles have potent anti-inflammatory properties and that targeting Siglec receptors with these nanoparticles represents a novel therapetic target for ALI.

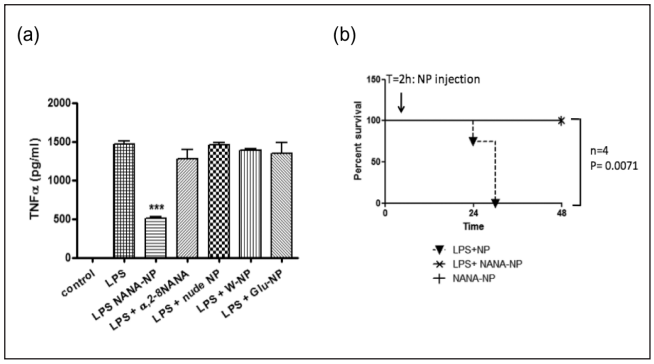

Figure 1a and 1b

British Thoracic Society Care Group Free Paper joint winner

The use of an inflammatory biomarker panel incorporating the BAL/blood ratio of monocytic surface TREM-1 in the diagnosis of ventilator-associated pneumonia

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Diagnosis of ventilator-associated pneumonia (VAP) is slow and fraught with difficulty. Biomarkers may speed up diagnosis. The triggering receptor expressed on myeloid cells-1 (TREM-1) is elevated in extracellular infections[1] and is a putative biomarker. It exists as a surface protein on monocytes and neutrophils, together with a soluble isoform. The diagnostic utility of bronchoalveolar lavage (BAL) soluble TREM-1 is controversial. No data exists on BAL surface TREM-1 in VAP. We investigated whether BAL surface TREM-1 expression increases in VAP and whether the BAL/blood ratio improves diagnostic accuracy. We also aimed to identify a diagnostic biomarker panel given that a single analyte is unlikely to classify all VAP cases.

Ninety-one adults were recruited into four groups and paired BAL and blood obtained: 27 with VAP (diagnosed by Clinical Pulmonary Infection Score and positive semi-quantitative microbiology), 18 ventilated without infection (ventilated control, VC), 15 ventilated with non-pulmonary infection (ventilated sepsis elsewhere, VSE) and 27 non-ventilated non-infected patients with chronic lung disease (non-ventilated control, NVC). Soluble biomarkers (IL-1β, IL-6, IL-8, soluble TREM-1 and procalcitonin) and surface markers (monocytic and neutrophilic surface TREM-1, CD11b and CD62L) were assayed in each sample, together with peripheral white cell count and CRP. Receiver-operator characteristic (ROC) curves were constructed for each marker. Data was assessed using the Kruskal-Wallis and Mann-Whitney tests, with Dunn's *post-hoc* analysis for multiple comparisons. The VAP group was compared to VC and VSE groups individually. As no significant difference existed, VC and VSE groups were combined into a non-VAP group. Fisher discriminant analysis was used to construct a diagnostic biomarker panel.[2]

Monocytic surface TREM-1 (mTREM-1) had an area under ROC curve (AUC) of 0.89 for diagnosing VAP, improving to 0.94 with the mTREM-1 BAL/blood ratio. Other individual markers had AUCs of 0.56-0.80. A six-marker panel incorporating the BAL/blood ratio of mTREM-1 and monocytic CD11b (mCD11b), BAL soluble TREM-1 and IL-1β, blood IL-6 and CRP differentiated VAP, non-VAP and NVC groups. For VAP, the AUC (95% CI) of this panel was 0.98 (0.96-1.00). Sensitivity, specificity and likelihood ratio (LR) were 95%, 93% and 12.9. Cross-validation and use of training and validation cohorts confirmed the robustness of the panel.

In conclusion, the BAL/blood ratio of surface mTREM-1 may be useful in VAP diagnosis and differentiation from non-pulmonary sepsis. A diagnostic biomarker panel incorporating the BAL/blood ratio of mTREM-1 and mCD11b, BAL soluble TREM-1 and IL-1β, blood IL-6 and CRP has clinical utility in identifying VAP.

Acknowledgements: We are grateful to the Westminster Medical School Research Trust, The National Institute of Academic Anaesthesia and the Chelsea and Westminster Health Charity for funding this project.

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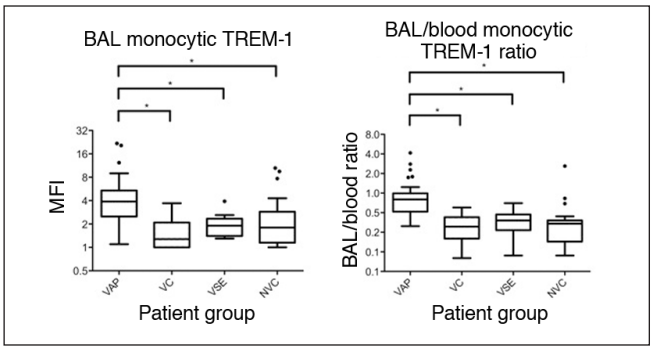

Figure. mTREM-1 expression in BAL and the BAL/blood ratio. Box-whisker (Tukey) plots of the BAL mTREM-1 levels and the BAL/blood ratio in VAP, Ventilated control (VC), Ventilated sepsis elsewhere (VSE) and non-ventilated control (NVC) patients. Medians and inter-quartile ranges are indicated. p<0.001 for all groups. MFI=mean fluorescent intensity derived from flow cytometry.

Research Prioritisation Exercise Presentation winner

Effects of electrical muscle stimulation on muscle wasting in patients receiving prolonged mechanical ventilation

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Muscle wasting in critically ill patients is common, often profound and associated with poor short and long term outcomes.[1] Early prevention of muscle wasting is a challenge and few, if any measures are available to reverse it.

Electrical muscle stimulation (EMS) is a simple method of inducing repetitive muscle contractions and has been shown to preserve muscle mass following immobilisation in other disease groups. In the post-operative catabolic state, EMS influences protein synthesis and degradation with associated maintenance of muscle morphology.[2] Recent studies in critically ill patients have shown conflicting results[3,4] and the precise mechanism by which it might be useful remains uncertain. This proof of concept study hopes to address the question as to whether EMS can affect changes in surrogate muscle protein biomarkers in critically ill patients subject to muscle wasting, whilst concomitantly preserving mass and strength. This will help elucidate the possible benefits and mechanism of action of EMS in critically ill patients.

Adult patients predicted to receive prolonged mechanical ventilation for longer than 72 hours will be randomised to twice daily low frequency EMS of bilateral upper and lower limbs for the duration of the intensive care unit (ICU) stay, or sham control. Ultrasonographic muscle cross sectional area of rectus femoris and biceps brachii, muscle strength and the Timed Up and Go test will be assessed at ICU and hospital discharge. In addition, urinary and serum muscle biomarkers will be measured daily. A sample size of 14 in each group will have 80% power to detect a difference in loss of 5.9% in muscle mass (the difference between an intervention group loss of 8.% and a control group loss of 13.9%[5] using a two group t-test with a 5% two-sided significance level. We aim to recruit 28 patients to the study.

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Cauldron Presentation winner

Brainstem death testing – confined to history

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Cauldron proposal: Diagnosing brainstem death on clinical testing alone is a historical compromise and will be deemed unfit-for-purpose within the next decade.

There is no statutory definition of death in the United Kingdom. Clinical practice is based on the premise that 'death entails the irreversible loss of the....capacity for consciousness, combined with ... the capacity to breathe'[1] and that these capacities reside in the brainstem. Loss of these brainstem capacities most commonly follows cardiac arrest and death is diagnosed on traditional cardio-respiratory criteria. For approximately 1000 patients a year, loss of brainstem reflexes precedes cardiac arrest and death is declared on the basis of bedside neurological testing in the presence of a beating heart. Any uncertainty as to the robustness of this diagnosis of 'brainstem death' (BSD) would undermine public confidence in the medical profession, expose doctors to the risk of criminal prosecution and immediately halt the organ transplant service.

Brain death in North America and BSD in Europe did not arise from sound scientific or philosophical principles but were defined to provide a legal and ethical framework for the removal of organs from patients with 'irreversible coma.'[2] Diagnosis on clinical testing was a pragmatic solution in an era without advanced neurological imaging.[3] There is no international consensus on the essential components of brainstem tests.[4] The interpretation and application of guidelines is inconsistent even within the UK.[5] BSD does not invariably quickly lead to cardiopulmonary death.[6,7] A patient diagnosed BSD when 15 weeks pregnant, was successfully supported for a further 107 days to enable fetal maturation. A recent case report purports to be the first describing how a patient regained brainstem function, including spontaneous respiration, 20 hours after a declaration of brain death.[8]

As evidence mounts that current practice is seriously flawed, either the diagnosis of BSD should be routinely substantiated with modern confirmatory tests or the concept be abandoned altogether. Confirmatory tests are mandatory in eleven European countries[4] but are only considered in the UK when high cervical spine or maxillofacial injuries preclude clinical testing. CT angiography is rapid, inexpensive and widely available even in non neurosurgical centres.[9,10] The alternative to reinforcing the concept of BSD would be to abandon it altogether. A public consultation could then be opened regarding the management of patients with irreversible coma and what society views are the necessary prerequisites to organ donation. Is it time to challenge the dead donor rule,[11] or should we focus our attention on donation after cardiac death?

The Code of Practice[1] states that 'although death is a process rather than an event, a definition of when that process reaches the point at which a living human being ceases to exist is necessary'. It is incumbent upon us as doctors to ensure that such a definition is robust and transparent. The diagnosis of death constitutes one of our most fundamental duties but one with which the public would be least forgiving should we get it wrong.

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