Institution: Queen Mary University of London

Unit of Assessment: A1 (Clinical Medicine)

Title of case study: Coagulopathy of trauma

1. Summary of the impact

The discovery of an early Acute Traumatic Coagulopathy (ATC, a syndrome of abnormal clotting after trauma) by Professor Brohi's team in 2000, and subsequent work building on that pivotal discovery, has led to [A] a new understanding of why patients bleed to death after severe injury and resulted in [B] a fundamental change in resuscitation strategy for acute bleeding patients ('Damage Control Resuscitation') that has led to [C] a 250-300 per cent improved survival in massively bleeding trauma patients. Discovering the character and mechanism of ATC has led to [D] new research in diagnostics and therapeutic opportunities to further improve outcomes. These rapid changes have led to [E] new forums for professional education and [F] improved public understanding of science and medicine.

2. Underpinning research

Trauma remains one of the world's biggest contributors to the global burden of disease. The increasing burden is highest in young adults and children, with 90,000 deaths each year in the EC in people under 30, half of which are due to bleeding. The UK mortality for bleeding trauma patients requiring a massive transfusion approaches 50 per cent.

Loss of clotting function in severe bleeding was known about before 2003. But up to this point it was thought to be a late phenomenon, primarily due to loss or dilution of coagulation factors. Bleeding patients initially received intravenous volume resuscitation with packed red cells or crystalloid solutions. Later (usually only after a massive transfusion), the volume of fluid would lead to a dilutional coagulopathy which would be identified using standard laboratory tests of coagulopathy and usually treated with a small dose of fresh frozen plasma. We now know that this is too little, too late – and Brohi's research has been the main driver for this dramatic shift in the management of bleeding trauma patients.

Discovery of Acute Traumatic Coagulopathy (ATC)

In 2000, Brohi performed a retrospective study analysing blood samples from trauma patients brought in by the Helicopter Emergency Medical Service at Barts Hospital. He identified that one in four patients already had an established coagulopathy on arrival and that, if present, it was associated with a four-fold increase in mortality. This study was submitted for publication in 2001. It took two years for *Journal of Trauma* to accept it, primarily because reviewers could not believe the results. Eventually published in 2003 [1], this work was subsequently replicated in studies in the USA, Europe and Australia. Brohi's team at Queen Mary have since focused on understanding the mechanisms underlying coagulopathy in trauma, characterisation of ATC, developing diagnostic tests for its identification and new therapies, and management strategies for its treatment. This work has been supported in part by a £2m NIHR Programme Grant for Applied Research.

Characterisation of ATC

The Centre for Trauma Sciences, led by Brohi, showed that ATC is an endogenous coagulopathy caused by a maladaptive response to severe trauma and blood loss [2]. They have discovered that ATC is a unique coagulopathy in that it is characterised by a systemic activation of anticoagulation and fibrinolysis [2]. Blood clots are therefore poorly formed and rapidly broken down. With collaborators, Brohi's team have identified a novel mechanism for coagulopathy – activation of the anticoagulant protein C pathway, which is a new target for drug discovery [3].

Diagnosis of ATC

Standard tests of coagulation in trauma are the laboratory tests of clotting activation, such as the prothrombin time (INR). Brohi's team have shown that these tests are not available in a timeframe that is able to effectively guide management in these rapidly bleeding patients [4]. They have also shown that it is impossible reliably to clinically predict who will get ATC and need a massive

transfusion [5]. Since ATC is primarily a problem of clot strength and clot breakdown, standard laboratory clotting times are insensitive to its presence. Brohi's group have shown that a newer diagnostic device – thromboelastography – can identify patients with ATC within five minutes of arrival in the A&E department and have determined a diagnostic threshold for this condition. They have also discovered, however, that these devices are insensitive to the clot breakdown component of ATC and that new diagnostics will be needed in this area [6].

Treatment of ATC

Discovery of the underlying mechanisms of ATC has led to new therapeutic approaches. Research by the Brohi group has shown that fibrinogen deficiency is a key early component of ATC. They have shown that this loss can be identified rapidly on thromboelastography and has the potential to improve clotting function and survival if replaced early [7].

3. References to the research

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4. Details of the impact

4a: Change in management paradigm

The discovery of ATC has led to the development of a new management strategy for patients with trauma-related bleeding – 'Damage Control Resuscitation'. A central tenet of this paradigm is 'Haemostatic Resuscitation' that targets ATC. Management has shifted dramatically from awaiting and managing late coagulopathy to correcting ATC immediately with rapid early administration of clotting factor therapies and avoiding haemodilution. This resuscitation strategy has been widely adopted internationally, in military and civilian arenas. See for example [8,9].

4b: Change in survival

Brohi's findings were first taken up by the British military, who saw potential dramatically to reduce mortality rates if treatment was targeted at ATC. Studies in the wars in Iraq and Afghanistan, for example, showed that this approach appears to reduce mortality in severely bleeding patients from 65 per cent to 19 per cent [10]. These are retrospective studies but have prompted prospective clinical trials, which are now ongoing [11]. Mortality rates for critical trauma patients in shock were nearly three times lower at our own (Barts) Major Trauma Centre than nationally (20 vs 55 per cent) when using a DCR approach to treatment [12]. These findings have been replicated

internationally [eg 13].

4c: Change in policy / guidance

Based on the evidence above, both the USA and UK Surgeon Generals issued 'general standing orders' during the wars in Iran and Afghanistan that the management of severe haemorrhage should target ATC with high-dose coagulation therapies. The US Air Force General subsequently testified to the US Senate that this resuscitation approach had saved lives [14]. Our work in developing a DCR transfusion protocol – called 'Code Red' has now been adopted by all major trauma centres in London and is being adopted nationally and internationally. This coagulation-centric approach has been incorporated into UK national transfusion guidelines from the Association of Anaesthetists of Great Britain and Ireland [15] and new European Guidelines on the management of major haemorrhage [16]. The global Advanced Trauma Life Support Manual updated in 2012 includes ATC-targeted therapy in its protocols [17]. This approach to bleeding in trauma is now also being applied to other forms of bleeding, most notably post-partum haemorrhage, another of the world's major causes of death due to haemorrhage [18].

4d: New research directions

New diagnostic tools

The work of Brohi's team has shown that ATC cannot be reliably predicted from clinical signs and existing tests. There has been renewed interested in emergency use of thromboelastography; many hospitals now have these devices in their resuscitation rooms. But the current generation of thromboelastography devices were not designed for the emergency environment. Manufacturers are developing a new generation of devices for this purpose and also for pre-hospital care. In particular, one manufacturer has developed a 'ruggedized' version of their device that has been deployed in Camp Bastion in Afghanistan as well as in other conflict zones around the world [19]. Major manufacturers have joined a consortium with Brohi to develop the next generation of machines and interfaces in the EU FP7 programme "TACTIC" [20].

New treatments

New treatments are being developed and evaluated specifically to treat ATC. In simplest form, many hospitals have now put protocols in place to have pre-thawed FFP in the trauma receiving room, and this is deployed on some helicopters including emergency teams in Afghanistan. Several clinical trials of blood-derived coagulation therapies directed at ATC are underway. We are conducting the pilot CRYOSTAT trial of early cryoprecipitate – the first joint military-civilian randomised controlled trial. A large RCT of high-dose platelet therapy is underway in the USA, and a trial of fibrinogen therapy delivered en-route in a helicopter is underway in Austria. A large international trial of the antifibrinolytic tranexamic acid has shown improved survival in bleeding trauma patients and is being widely adopted worldwide [21]. Several pharmaceutical companies are developing new anti-ATC therapeutics, including Octapharma, Astra-Zeneca and CSL-Behring.

New research

The name 'Acute Traumatic Coagulopathy' was ratified in a consensus conference held on this coagulopathy in Chicago in 2008 [22]. A further consensus conference on coagulopathy in trauma was subsequently held jointly by the US National Institutes for Health (NHLBI) and the Department of Defence in Washington DC in 2010 [23], and again in Toronto in 2012. This led to several specific grant calls for research into trauma haemorrhage, including a large-scale programme from the US Army Combat Casualty Care programme. Through such funding, Brohi and others have developed experimental models of ATC to determine underlying mechanisms, identify new targets for drug discovery and evaluate new treatments. Large-scale human studies to elucidate mechanisms and underlying propensities for ATC are underway in Europe and USA, and renewed interest in bleeding in trauma has led to the development of research networks and a general upswing in the volume and quality of trauma research.

4e: Professional education

New educational initiatives have been formed for dissemination of these findings, including the 'PerioperativeBleeding.org' (Austria, Germany), the 'International Symposium on Critical Bleeding' (Europe and North America), 'Educational Initiative for Critical Bleeding in Trauma' (international)

[22], and a 'Trauma Coagulopathy & Transfusion Masterclass' at the London Trauma Conference.

4f: Improved public understanding of science

Brohi's work on ATC and new resuscitation protocols was featured in *New Scientist* "Code Red" [24] and in television programmes in the Netherlands and Australia. The team have showcased their work to the public at the Royal Society's Summer Science event 2011 [25] and the Big Bang Fair in Birmingham 2012.

5. Sources to corroborate the impact

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