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DISSERTATION

Damage Control Resuscitation: Systematic Review

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1.

Introduction

1.1 THE EVOLUTION OF THE DAMAGE CONTROL RESUSCITATION CONCEPT

Military conflicts often drive innovations in health care. The first and second world war and the Vietnam war saw significant advances in the care of the sick and injured, which were subsequently translated into civilian practice. The recent conflicts in Iraq and Afghanistan are no exception.[1][2] The intensity of warfare and types of munitions used has led to sustained numbers of casualties with high trauma burdens, and provided the stimulus for the development of new paradigms of care.[1] Damage control resuscitation is the synthesis of this collective experience.[3]

Exsanguination is the second commonest cause of death following trauma,[4] and unlike central nervous system injury, often preventable. Conventional resuscitation algorithms based on the sequential use of crystalloids and colloids, followed by packed red blood cells and then plasma or platelet transfusions, were based on the belief that coagulopathy developed over the course of several hours.[5] As a consequence, resuscitation was focused on the restoration of cardiac output and end-organ perfusion, with volume expansion; and oxygen delivery, with transfusion of packed red blood cells.[6] The management of coagulopathy and hypothermia, even in the context of damage control surgery, was deferred until measurable abnormalities were present. This approach has been in widespread use since the 1980s and is codified in the Advanced Trauma Life Support programme.[5]

Damage control resuscitation, in contrast, is a management strategy which addresses the entire lethal triad of coagulopathy, acidosis, and hypothermia immediately upon admission, rather than sequentially.[3][7] It is a development and refinement of the damage control surgery concept, based on a better understanding of the pathophysiology of major trauma. Although pioneered by military surgeons, damage control resuscitation is not only applicable to injuries sustained in war. The impressive improvements in outcome witnessed in the military setting [8][9][10] have been translated into civilian practice, and followed by the rapid acceptance of damage control resuscitation by trauma surgeons worldwide.

The damage control surgery concept was founded on the realisation that – provided surgically correctable haemostasis had been achieved – trauma patients died of the metabolic consequences of injury. The discovery of the mutually perpetuating “lethal triad” or “bloody vicious circle” of coagulopathy, metabolic acidosis, and hypothermia led to the introduction of a surgical strategy which sacrificed the completeness of the immediate repair in order to address the combined

physiological impact of injury and operation, and avoid progression to metabolic unsalvageability.[10][12] The notion that resuscitation could not take place at the same time as surgery resulted in the rigid stratification of damage control surgery into phases of management – surgery followed by resuscitation.[10] A new understanding of the aetiology of acute traumatic coagulopathy, and its impact on survival, led to the re-evaluation of this concept.

The coagulopathy of trauma was classically viewed as a byproduct of resuscitation, attributed to consumption, dilution and dysfunction (due to acidosis and hypothermia) of procoagulant serine proteases. It is now recognised that injury-related coagulopathy is often present prior to admission, and before any fluid or blood product administration, and thus cannot be caused by dilution alone, or even to a significant extent. This early coagulopathy appears to be related to hypoperfusion, is distinct from disseminated intravascular coagulopathy, and has been termed Acute Coagulopathy of Trauma-Shock (ACoTS).[13][14] Recognition of the pivotal role of ACoTS in determining outcome has led to the adoption of so-called haemostatic resuscitation strategies, which involve the administration of fresh frozen plasma and platelets in predefined ratios with packed red blood cells, effectively reconstituting whole blood, with the aim of normalising all three aspects of the lethal triad – ideally before the patient leaves the operating theatre.[3][7] Damage control resuscitation is surgery and resuscitation, performed concurrently, with close cooperation between anaesthetist and surgeon.[3][7]

The components of damage control resuscitation remain vaguely defined, but in combination appear to improve the survival of the most severely injured patients. The rapid introduction and evolution of the components of damage control resuscitation, without formal evaluation in interventional studies, is explained by the needs and demands of the operational military setting which spawned its development. There is thus an urgent need for a review and appraisal of the evidence supporting damage control resuscitation.

1.2 OBJECTIVES

The objectives of this dissertation are

- To define damage control resuscitation
- To conduct a systematic review of the evidence for damage control resuscitation

1.3 PREVIOUS REVIEWS AND GUIDELINES

There is a rapidly expanding body of literature on damage control resuscitation. Almost every edition of the Journal of Trauma seems to carry an article on the subject, and there have been several key publications, such as Holcomb's editorials "Damage control resuscitation" and "Damage control resuscitation: directly addressing the coagulopathy of trauma", and an ever-increasing number of non-systematic reviews. [3][7][14][15][16][17] To date, however, there have been no *systematic* reviews of the damage control resuscitation strategy, and although there are many existing clinical guidelines on the management of trauma and major haemorrhage, the vast majority are not evidence-based either, and none specifically address the recent developments which constitute damage control resuscitation.[18][19]

1.4 THE RATIONALE FOR SYSTEMATIC REVIEW

A systematic review identifies, evaluates and assimilates evidence on the effectiveness of interventions, with the aim of assessing the consistency and generalisability of research findings.[20] Reviews based on unsystematic literature surveys or expert opinion are liable to bias.[21][22]

Systematic reviews form the basis for meta-analyses and clinical guidelines. Modern clinical guidelines must be explicitly linked to supporting evidence and therefore rely heavily on a thorough and unbiased review of the literature.[22][24][25] Meta-analysis is an extension of systematic review, mathematically re-analysing data from primary studies, and thus depends on the appropriate identification and selection of primary research. Organisations such as the Cochrane Collaboration, the Scottish Intercollegiate Guidelines Network (SIGN), and the National Institute for Health and Clinical Excellence (NICE) have contributed a great deal to advancing systematic review methodology.

The essential criteria of a systematic review are an explicit search strategy, selection of literature according to defined inclusion and exclusion criteria, and evaluation against consistent standards.[22]

1.5 TERMINOLOGY

For the purpose of this work, “trauma”, “trauma surgery” and “trauma surgeon” are defined as relating to injuries sustained to the torso, neck, and vasculature of the limbs, not the management of isolated musculoskeletal injuries.

1.6 TARGET USERS

This dissertation is not intended to be a textbook or manual of trauma surgery. It is assumed that the reader is familiar with the principles of resuscitation and trauma surgical techniques.

1.7 TARGET PATIENTS AND SETTING

This review relates to patients with haemorrhagic shock due to trauma, managed in the setting of a European or North American centre, by general surgeons and anaesthetists with an interest and experience in trauma care. Hospitals should be large enough to be able to provide on-site blood transfusion services and intensive care facilities.

2.

Methods

2.1 OVERVIEW OF METHODOLOGY

Systematic reviews aim to minimise bias by using explicit methods to identify and collate all existing evidence in order to address a specific research question.[26] The processes of identification and appraisal of evidence must be methodical and reproducible. The methodology used in this dissertation is based on a synthesis of techniques employed by the Cochrane Collaboration, the Scottish Intercollegiate Guidelines Network, and the National Institute for Health and Clinical Excellence, but also incorporates aspects of the MERGE (Method for Evaluating Research and Guideline Evidence), and AGREE (Appraisal of Guidelines for Research & Evaluation) initiatives. [22][26][27]

The development of a systematic review can be broken down into several steps, which include the setting of specific research questions, the identification and appraisal of evidence, and the formation of evidence statements.

2.2 KEY QUESTIONS

The first step in the writing of a systematic review is to divide the subject area into a number of key questions.[26] The selection of a set of clear and focused queries with specified and clinically relevant outcomes – such as survival, rather than surrogate measures, eg. change in blood pressure – is fundamental to the success of the review.[26] The questions chosen for this review, grouped by subject area, are:

Haemostatic resuscitation

- Is the early and aggressive use of fresh frozen plasma in predefined ratios with packed red blood cells associated with increased survival of trauma patients?
- Is the early and aggressive use of platelets in predefined ratios with packed red blood cells associated with increased survival of trauma patients?
- Does factor VIIa improve survival in trauma patients with severe bleeding?
- Does factor VIIa reduce transfusion requirements in trauma patients?
- Does the use of cryoprecipitate improve survival in trauma patients?
- Does tranexamic acid reduce transfusion requirements and/or mortality in trauma patients?

Permissive hypotension

- Does a strategy of withholding or limiting fluid resuscitation prior to surgical control of haemorrhage improve survival?

Acidaemia management

- Does the administration of tris-hydroxymethyl aminomethane (THAM) improve survival in trauma patients?

Hypothermia mitigation

- Do aggressive attempts at hypothermia mitigation improve outcome in trauma patients?
- What is the most effective method of preventing and treating hypothermia in trauma patients?

Damage control surgery

- Does the use of damage control surgical techniques improve survival in trauma patients with severe bleeding?

Indications

- What are the indications for initiating damage control resuscitation?

2.3 OUTCOME MEASURES

The outcome measure chosen to answer the majority of the key questions in this review was survival (or its reciprocal, mortality). Mortality is always clinically significant, and relatively easy to measure, although it is accepted that studies attempting to show differences in mortality require large numbers of patients, and may be the subject of type II errors.

2.4 IDENTIFICATION OF EVIDENCE

2.4.1 Search strategies

The literature search was designed to focus on the best available evidence, addressing each key question in turn. In order to maximise coverage and minimise bias, searches were conducted across the medline and embase medical literature databases, and the Cochrane library. Where appropriate, search filters were used, but in general, search strategies were designed to maximise sensitivity, while accepting low precision, as recommended by the Cochrane Collaboration.[26] In order to capture the breadth of the subject, separate searches for primary studies, secondary research, and existing guidelines were conducted, but secondary literature and existing guidelines were only considered for inclusion when based on systematic methodology. Searches

were limited to articles in English and German, and published after 1980 (except in the case of damage control surgery, as several key papers on this subject were published in the late 1970s). Animal studies were not considered. Although there is a substantial body of literature on animal models of resuscitation and treatment, these are contentious, and the applicability of animal studies to human physiology is questionable.[28]

2.4.2 Sifting of search output

The medline and embase database search output was then assessed for eligibility. Citation lists were initially sifted for irrelevant material, and titles that were not relevant to the key question eliminated. The abstracts of the remaining papers were then examined using inclusion and exclusion criteria, and studies with inappropriate designs excluded. The use of such criteria helps to minimise bias.[26] Articles were acquired on completion of the sifting process. However, in acknowledgement of the limitations of databases and search strategies, computerised searches were supplemented by manual cross-referencing. The strategy is summarised diagrammatically in fig 1.

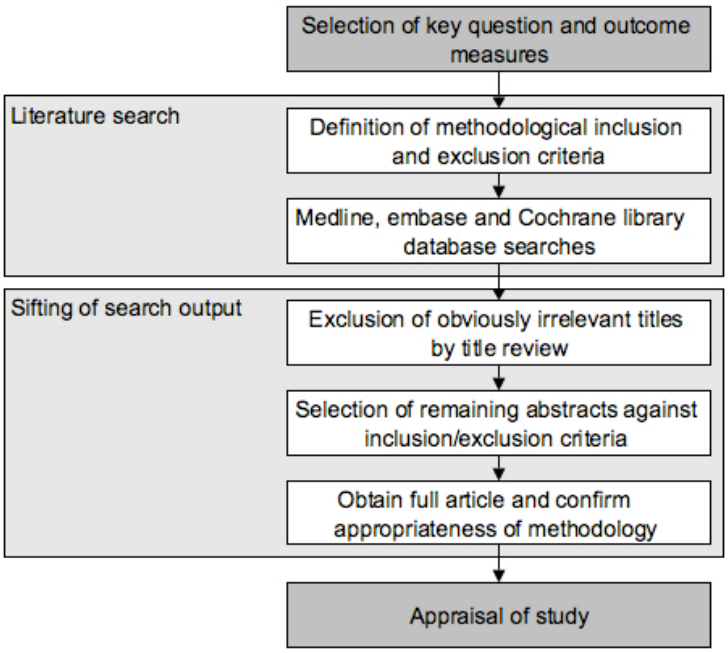

Fig 1. Identification of evidence

2.5 APPRAISAL OF EVIDENCE

Following selection of articles as potential sources of evidence, the methodological validity of each study was assessed. The results of this assessment determine the level of evidence allocated to the study.[22]

2.5.1 MERGE checklists

Methodological assessment must be based on aspects of study design which have been shown to influence the validity of the results reported and conclusions drawn, and varies between different study types.[22] Primary research and systematic reviews were appraised using the MERGE (Method for Evaluating Research and Guideline Evidence) criteria, which have been the subject of wide consultation and evaluation.[22][23] These criteria are endorsed by the Scottish Intercollegiate Guidelines Network and National Institute of Clinical Excellence for the purpose of evaluating supporting evidence for guideline development.[22][29] MERGE checklists are available for all principal study designs (systematic reviews and meta-analyses, randomised trials, cohort studies, case-control studies, and studies of diagnostic accuracy), and consist of three sections, providing a focused description of the results, an assessment of internal validity, and an overall assessment of the methodological quality of the study, indicated by a rating of "++", "+", or "-". A "++" rating indicates that *all or most* of the assessed criteria have been fulfilled. Unfulfilled criteria are thought *very unlikely* to alter the conclusions of the study. A "+" rating indicates that *some* of the assessed criteria have been fulfilled. Unfulfilled criteria are thought *unlikely* to alter the conclusions of the study. A "-" rating indicates that *few or no* criteria were fulfilled, and that the conclusions of the study are *likely or very likely* to alter.[22] The methodology checklist proformas for randomised controlled trials and cohort studies are shown in figs 2 and 3. Due to constraints of space, the completed methodology checklists are not included with this dissertation, but their conclusions are reproduced in the evidence tables (see below).

Section 1: Internal Validity			
1.1	The study addresses an appropriate and clearly focused question.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.2	The assignment of subjects to treatment groups is randomised.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.3	An adequate concealment method is used.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.4	Subjects and investigators are kept "blind" about treatment allocation.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.5	The treatment and control groups are similar at the start of the trial.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.6	The only difference between groups is the treatment under investigation.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.7	All relevant outcomes are measured in a standard, valid, and reliable way.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.8	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?		
1.9	All the subjects are analysed in the groups to which they are randomly allocated (intention-to-treat-analysis)	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable

Section 2: Overall Assessment		
2.1	How well was the study done to minimise the risk of bias or confounding, and to establish a causal relationship between exposure and effect?	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated?	
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	

Section 3: Description		
3.1	How many patients are included in this study?	
3.2	What are the main characteristics of the patient population?	
3.3	What intervention is being investigated in this study?	
3.4	What comparisons are being made in the study?	
3.5	For how long are the patients being followed up in the study?	
3.6	What outcome measure(s) are used in the study?	
3.7	What size of effect is identified in the study?	
3.8	How was this study funded?	
3.9	Does this study help to answer your key question?	

Fig. 3 MERGE criteria and checklist for randomised controlled trials

Section 1: Internal Validity			
1.1	The study addresses an appropriate and clearly focused question.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
Selection of subjects			
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.		
1.6	Comparison is made between full participants and those lost to follow-up, by exposure status.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
Assessment			
1.7	The outcomes are clearly defined.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.8	The assessment of outcome is made blind to exposure status.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.10	The measure of assessment of exposure is realiable.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
1.12	Exposure level of prognostic factor is assessed more than once.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
Confounding			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable
Statistical analysis			
1.14	Confidence intervals are provided.	☐ Well addressed ☐ Adequately addressed ☐ Poorly addressed	☐ Not addressed ☐ Not reported ☐ Not applicable

Section 2: Overall Assessment		
2.1	How well was the study done to minimise the risk of bias or confounding, and to establish a causal relationship between exposure and effect?	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the exposure being investigated?	
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	

Section 3: Description		
3.1	How many patients are included in this study?	
3.2	What are the main characteristics of the patient population?	
3.3	What environmental or prognostic factor is being investigated in this study?	
3.4	What comparisons are being made in the study?	
3.5	For how long are the patients being followed up in the study?	
3.6	What outcome measure(s) are used in the study?	
3.7	What size of effect is identified in the study?	
3.8	How was this study funded?	
3.9	Does this study help to answer your key question?	

Fig.4 MERGE criteria and checklist for cohort studies

2.5.2 AGREE instrument

Existing guidelines were also considered for inclusion in the evidence base, following methodological evaluation using the AGREE (Appraisal of Guidelines, Research and Evaluation for Europe) instrument for the assessment of clinical practice guidelines.[27] The AGREE instrument provides an assessment of the predicted validity of a guideline, ie. the likelihood that it will achieve its intended outcome. AGREE consists of 23 items organised in six domains. Each domain is intended to capture a separate dimension of guideline quality. “Scope and purpose” is concerned with the overall aim of the guideline, the specific clinical questions and the target patient population. “Stakeholder involvement” focuses on the extent to which the guideline represents the views of its intended users. “Rigour of development” relates to the process used to gather and synthesise the evidence, the methods to formulate the recommendations and to update them. “Clarity and presentation” deals with the language and format of the guideline. “Applicability” pertains to the likely organisational, behavioural and cost implications of applying the guideline. “Editorial independence” is concerned with the independence of the recommendations and acknowledgement of possible conflict of interest from the guideline development group. Each item is scored, by each appraiser, on a scale ranging from 4 (“strongly agree”) to 1 (“strongly disagree”), with the midpoints 2 (“disagree”) and 3 (“agree”). The number of appraisers is flexible. The standardised composite percentage score for each domain is calculated using the formula 100x (obtained score – minimum possible score)/(maximum possible score – minimum possible score). The six domain scores are independent and cannot be aggregated into a single quality score. “Overall assessment” is a recommendation as to whether the guideline in question should be used in practice, and is graded as “++” (strongly recommended), “+” (recommended with provisos), or “-“ (not recommended).[27]

2.5.3 Minimising bias

Although predefined inclusion and exclusion criteria and the use of tools such as the MERGE checklists and the AGREE instrument objectify the assessment process, an inevitable degree of subjective judgement remains. This is usually minimised through dual or multiple assessment and consensus between appraisers. Such a multi-author process would not be appropriate for a dissertation and has therefore been omitted.

2.6 FORMING EVIDENCE STATEMENTS

2.6.1 Considered judgement

The results of the assessments of individual studies were compiled in evidence tables, which summarise the findings and quality of articles relating to each key question. The level of the evidence is determined by an objective assessment of the design and quality of each individual study and a more subjective judgement on the consistency, clinical relevance and external validity of the whole body of evidence.[22] It is rare for the evidence to show clearly and unambiguously what course of action should be recommended for any given problem. In order to address this problem, the Scottish Intercollegiate Guidelines Network have introduced the concept of "considered judgement".[22] Considered judgement is a review of the *total body of evidence* covered by the evidence tables, consisting of an appraisal of the quantity, quality, and consistency of evidence; the external validity (generalisability) of studies, and the applicability to the target population. The process culminates in the formulation of a summary, known as an evidence statement, and the assignment of a level of evidence. Evidence statements are based entirely on the evidence presented, and do not take into account material which has not been covered as part of the systematic review.

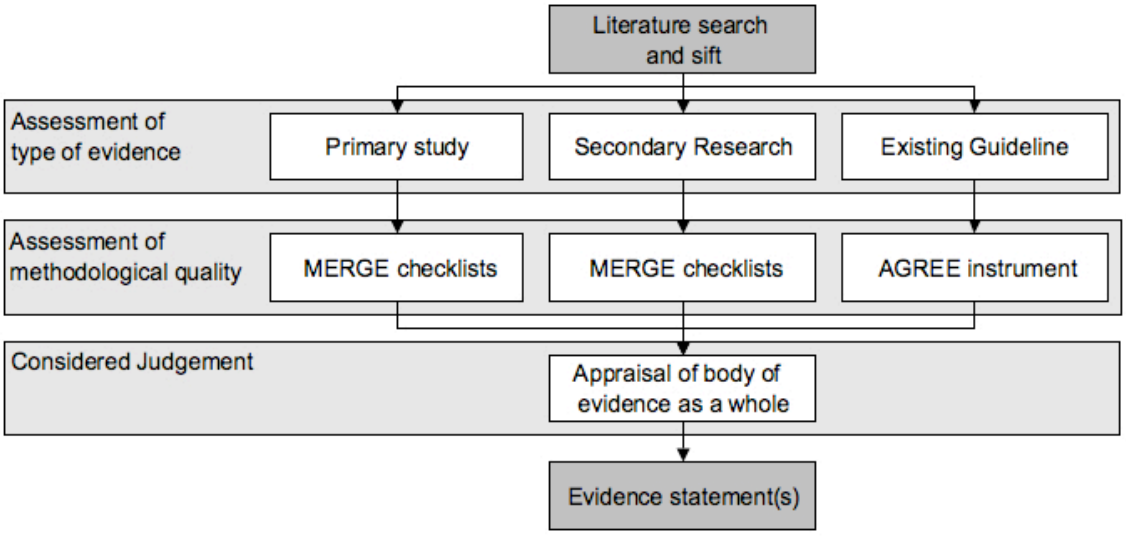

Fig 4. Forming evidence statements

2.6.2 Assigning levels of evidence

Assigning an evidence level to a statement quantifies the strength of the supporting evidence. There are several systems in use. The US Agency for Health Care Policy and Research (AHCPR, now the US Agency for Health Research and Quality, AHRQ) system is one of the oldest, and

was widely used for many years, but has limitations. An alternative system proposed by the Scottish Intercollegiate Guidelines Network in 2000 was developed specifically for the purpose of linking evidence to practice recommendations in guidelines, but separates levels of supporting evidence from the grade of recommendations.[30] The SIGN system emphasises consideration of the body of evidence *as a whole*. It is more flexible than the AHCPR/AHRQ system, because it allows more weight to be given to good quality observational studies, where RCTs are not available for ethical or practical reasons, as is often the case in trauma care. The SIGN system is sometimes still difficult to apply in practice, but is an improvement on the AHCPR/AHRQ system, and therefore used throughout this dissertation. It is summarised in table 1.

Table 1: SIGN system for assigning levels of evidence [30]

Level of evidence	Type of evidence
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies High-quality case control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderated probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus

2.7 FORMAT OF THIS DISSERTATION

2.7.1 Outline structure

This dissertation constitutes secondary research, evaluating and analysing existing work, and the format has been adapted accordingly. The "introduction" and "methodology" sections have already been covered and are broadly similar to a dissertation reporting experimental work. Given the non-experimental nature of this work, a "hypothesis" has been omitted and substituted

with “objectives” (section 1.2). The “systematic review” section effectively represents the “results” section of a conventional thesis. It is followed by a “discussion” which summarises and contextualises the findings derived in the “results” section, identifies areas of practice for which evidence is lacking, and examines the validity of the review and applicability of the findings. The “conclusions” section (4.3) is self-explanatory and equivalent to a conventional dissertation.

2.7.2 Presentation

The aim of the systematic review chapter is to answer the key questions. For clarity, the chapter is broken down into six parts: Haemostatic resuscitation, hypotensive resuscitation, acidaemia management, hypothermia management, damage control surgery and indications. Some of these parts contain more than one subsection, such as “fresh frozen plasma” under “haemostatic resuscitation”.

The subsections commence with a specific, non-systematically developed introduction, followed by the key question, and the outcome measure(s) chosen. The next paragraph contains a description of the search strategy and output for relevant primary research, and a summary of the evidence (as an evidence table), derived from MERGE checklists (which, for reasons of space, are not included with this dissertation, see above). Evidence tables differ slightly for interventional/observational studies, secondary research, and existing guidelines. Each table contains the bibliographic reference to the publication, the summary rating (++, +, or -), and several columns describing the results. This is followed by an additional row summarising any particular issues of the study, in longhand. A similar format is employed for secondary research and existing guidelines. The selection of the literature is also summarised in a flow diagram at the end of each section.

This combined body of evidence is then appraised in the “considered judgement” paragraph. Each subsection concludes with one or more “evidence statements”, which summarise the available evidence. The level of evidence assigned is given in the right margin.

3.

Systematic Review

3.1 DEFINITION

Damage control resuscitation is a composite, multimodal, multidisciplinary strategy for the management of the exsanguinating trauma patient, consisting of haemostatic resuscitation, permissive hypotension, acidaemia management, hypothermia management, and damage control surgery.[3][7][15][16][31]

3.2 HAEMOSTATIC RESUSCITATION

Haemostatic resuscitation is the early use of blood components in predefined ratios, and the adjunctive use of therapies such as recombinant factor VIIa and antifibrinolytics, to avert the consequences of traumatic coagulopathy. This section outlines the aetiology and diagnosis of traumatic coagulopathy, and systematically reviews the evidence for these management strategies.

3.2.1 Aetiology of traumatic coagulopathy

Prevalence

Traumatic coagulopathy was traditionally regarded as a consequence of resuscitation, occurring some hours after injury. Recent studies have shown that this is not the case, and that coagulopathy may be present as early as on admission to hospital, and is therefore not the result of fluid administration alone. Brohi et al conducted a retrospective review of 1,088 trauma patients (median ISS 20, 57.7% ISS>15) over a five-year period. 24.4% of patients were coagulopathic (defined as a prothrombin time or activated partial thromboplastin time 1.5x greater than normal) on admission. This finding was associated with a four-fold increase in mortality (46% vs 11%, $p<0.001$).[32] In a similar review comprising 7638 patients, MacLeod et al also showed that abnormal prothrombin time (>14s) and partial thromboplastin time (>34 s) on admission were independent predictors of mortality (median ISS of 9, odds ratio for death 3.6, 95% confidence interval 3.15-4.08, $p<0.0001$), and an analysis of data from the German Trauma Registry revealed a prevalence of 34.2% (based on a prothrombin time test of <70%).[33][34] Although these studies comprised different groups of patients, with different patterns and severity of injury, and utilised different definitions of coagulopathy, they all showed that coagulopathy is present, on admission, in a substantial proportion of trauma patients, and is associated with decreased odds of survival.

Novel concepts

Traumatic coagulopathy is a complex, dynamic, multifactorial process, involving all components of the haemostatic system, and the simplistic traditional explanations of traumatic coagulopathy which pervade the literature are no longer sufficient to characterise the condition or to base treatment decisions on. [14] The regulation of fibrin generation, platelets, and endothelium all play a role, together with inhibition of stable clot formation by anticoagulant and fibrinolytic processes.[14] Which of these mechanisms predominates depends on the nature and severity of the injury, the effects of therapy, and the chronicity of wounding and treatment.[14] The Educational Initiative on Critical Bleeding in Trauma (EICBT), an independent international think-tank, describes six key initiators of coagulopathy in trauma patients: Tissue trauma, shock, haemodilution, hypothermia, acidaemia, inflammation. [14] While this model provides a useful framework, it is more helpful to divide these six mechanisms into two initiators (tissue injury and shock), and four propagators (haemodilution, hypothermia, acidosis, and inflammation).

Initiators

Tissue injury initiates both coagulation and fibrinolysis, but in isolation is rarely responsible for clinically overt coagulopathy.[14] Endothelial damage leads to exposure of subendothelial type III collagen and tissue factor, which bind von Willebrand factor, platelets, and activated factor VII.[35] The tissue factor/factor VIIa complex then activates serine proteases, ultimately resulting in thrombin and fibrin formation.[36] Hyperfibrinolysis is a consequence of both tissue injury and shock.[13] The presence of thrombin increases the expression of tissue plasminogen activator (tPA) by endothelium, and endothelial injury – physical or ischaemic – releases tPA, promoting fibrinolysis.[37][38][39][40] The effects are exacerbated by the inhibition of plasminogen activator inhibitor-1 (PAI-1).[41] The purpose of hyperfibrinolysis in trauma is presumably to limit clot propagation to the site of vascular injury.[14] With widespread trauma and endothelial activation, however, such localisation may be lost.[14] Recognition of the contribution of hyperfibrinolysis to the clinical syndrome of traumatic coagulopathy is important, as it opens up new therapeutic possibilities: Antifibrinolytic drugs, such as tranexamic acid, have been used successfully in elective surgery for some time, and may prove to be a useful adjunct in traumatic haemorrhage.

Although coagulopathy and fibrinolysis are initiated by tissue injury, the main driver of traumatic coagulopathy appears to be shock, or more accurately, systemic hypoperfusion. An elegant recent study showed that patients without shock are rarely coagulopathic, even after major mechanical trauma (as measured by ISS). [41] In contrast, there is a dose-dependent

relationship between the severity of shock/ tissue hypoperfusion – as measured by base excess – and the degree of admission coagulopathy, as measured by prothrombin time (PT) and activated partial thromboplastin time (APTT).[41][42] All of these derangements were determined before fluid resuscitation, and are therefore not attributable to haemodilution. The pathophysiology of this process is distinct from that of disseminated intravascular coagulation (DIC), leading the Educational Initiative on Critical Bleeding in Trauma to coin the term "Acute Coagulopathy of Trauma-Shock" (AcoTS).

Despite these exciting new realisations and novel terminology, many aspects of the underlying mechanisms remain unclear. While acidaemia is well known to interfere with protease function, clinical coagulopathy is evident at milder degrees of acidaemia than have been identified as causing significant loss of protease activity.[14] It is conceivable that hypoperfusion results in widespread endothelial disruption or activation, which in turn causes dysregulation and activation of coagulation and fibrinolysis.[14] Brohi et al have implicated activated protein C (aPC) in this process, but this was inferred by association rather than direct measurement of aPC levels.[41] Formation of anticoagulant thrombin, through complexation with thrombomodulin, would also result in hyperfibrinolysis, either due to aPC consumption of PAI-1, or reduced activation of thrombin-activatable fibrinolysis inhibitor.[43][44][45] More work is required before these mechanisms become fully elucidated, however, there is little doubt that, in combination, tissue trauma and systemic hypoperfusion are the prime initiators of traumatic coagulopathy in the immediate postinjury phase.

Propagators

The initial coagulopathy may then be propagated and exacerbated by the physical and physiological impact of haemodilution, acidosis, hypothermia, and inflammation.[14] Reduced intravascular hydrostatic pressure results in shifts of fluid devoid of coagulation factors from the extracellular and interstitial spaces into the intravascular compartment.[14] This effect is compounded by volume expansion with synthetic fluids. The effects of crystalloid administration on coagulation have been demonstrated in mathematical models, in vitro, and in volunteer studies.[46][47][48][49] Colloids, in addition to their disproportionately greater dilutional effects, may in addition interfere directly with clot formation and stability.[14] Packed red blood cell administration also results in dilution of clotting factors. [46][50][51]

Traumatic coagulopathy is exacerbated further by hypothermia, which inhibits protease activity and platelet function, although the latter appears to predominate.[52] Acidosis, the consequence

of anaerobic metabolism precipitated by hypoperfusion as well as iatrogenic chloride administration, also impairs protease function.

Implications for clinical practice

Although incomplete, an emerging understanding of the mechanisms underlying the Acute Coagulopathy of Trauma Shock forms the basis of haemostatic resuscitation. Historically, whole blood was the preferred therapy for patients with exsanguinating trauma. In the late 1980s, concerns about resource utilisation and infectious disease transmission led to a switch to component therapy, which aims to correct measured deficiencies. This approach of replacing specific haemotological deficits, extrapolated from elective surgical practice, extended into guidelines for patients requiring massive transfusion after injury, although proof of the efficacy of this change in practice was lacking.[46][48][53][54][55] Many transfusion guidelines continue to recommend against the administration of clotting factors until the prothrombin or activated partial thromboplastin time is greater than 1.5x normal, [19][55][56][57][58] and perpetuation of this type of "expert opinion" is in part responsible for the common finding of refractory coagulopathy in trauma patients.[46]

Increasing experience with large numbers of severely injured patients has led to a greater appreciation of the importance of the early coagulopathy of trauma. Several recent studies have shown that a more proactive strategy, administering packed red cells, fresh frozen plasma and platelets in similar ratios to those found in whole blood, may be associated with increased survival.[59][60][61][62][63]

Diagnosis

Although the diagnosis of traumatic coagulopathy is, at first sight, straightforward, this is not the case. Prothrombin time and partial thromboplastin time measurement is readily available and widely used. Indeed, all three of the recently published large retrospective studies of traumatic coagulopathy mentioned above relied on these tests for the diagnosis of coagulopathy.[32][33][34] However, these surveys were designed to establish the prevalence and clinical significance of traumatic coagulopathy, rather than the diagnostic accuracy of prothrombin time and partial thromboplastin time. Although these studies show that an abnormal prothrombin and partial thromboplastin time is associated with adverse outcome, they do not validate the tests: Patients who had normal prothrombin and partial thromboplastin times could still have been clinically coagulopathic.

The limitations of prothrombin time and partial thromboplastin time measurements are well recognised. These assays only measure the functioning of isolated aspects, rather than the global

performance, of the coagulation system.[16][64] In particular, the reactions are conducted on platelet-poor plasma and thus do not evaluate the cellular interactions of coagulation.[16][64] Prothrombin time and partial thromboplastin time measurements are furthermore conducted at 37^{o}C, at supraphysiological calcium concentrations, and therefore do not reflect the in vivo effects of hypothermia or hypocalcaemia.[64][65] In addition to limited validity, prothrombin time and partial thromboplastin time measurements are time-consuming, both intrinsically, and because they are usually performed in a central laboratory rather than at the bedside, necessitating the transport of specimens.[51] A further drawback of partial thromboplastin time and prothrombin time measurement is their inability to identify a hypercoagulable state.

Many authorities therefore now agree that the initial diagnosis of traumatic coagulopathy should not rest on the demonstration of abnormal in vitro coagulation parameters, [7][16][51][64][65] [66][67] although these tests may have a role in monitoring the response to treatment.

Thromboelastography (TEG®) measures shear elastic modulus during clot formation and subsequent fibrinolysis. In contrast to prothrombin time and partial thromboplastin time, thromboelastography provides a global functional profile of whole blood coagulation, providing information on the initiation of coagulation, propagation kinetics, fibrin-platelet interaction, clot firmness and fibrinolysis.[68][69][70] It can also be performed at the temperature of the patient, reflecting the effect of hypothermia on clotting.

Thromboelastography provides a graphic output, from which a variety of parameters can be derived, and has been shown to be a more sensitive measure of coagulation disorders than standard tests of coagulation.[71] The ability to diagnose and characterise hyperfibrinolysis, now recognised to play a major role in traumatic coagulopathy, has led to renewed interest in this technique. There is a large volume of literature relating to the use of TEG® in orthotopic liver transplant and cardiac surgery,[17] but despite its advantages, thromboelastography has not become the standard of care. This is largely related to the cost and delicate nature of the equipment, which requires considerable training and maintenance. A new device, the rotation thromboelastogram analyzer (ROTEM®, Pentapharm, Munich, Germany), appears to have overcome some of the limitations of classic thromboelastography, and is also faster.[70] A basic ROTEM® analysis takes approximately 15 mins, although the characterisation of fibrinolysis is more time consuming.[70] Several small, recent studies have confirmed the utility of ROTEM® in trauma management.[68][69][70][72] Further studies are needed, but thromboelastography has the potential to provide a better and faster characterisation of traumatic coagulopathy than

other tests currently in use, and its ability to differentiate hyperfibrinolysis from factor and platelet deficiency is of particular interest.

However, until ROTEM® becomes more widely available, and experience accumulates, the diagnosis of traumatic coagulopathy, and the initiation of appropriate management, must be made on clinical grounds.

3.2.2 Fresh frozen plasma

The publication of Brohi's and MacLeod's observational studies coincided with the beginning of the Iraq war,[32][33] and led American military surgeons to experiment with the use fresh frozen plasma as a primary resuscitation fluid. The unprecedented severity of injuries inflicted by modern munitions and improvised explosive devices resulted in a high incidence of traumatic coagulopathy and exsanguination from microvascular bleeding despite surgical control of haemorrhage. Severely injured patients predicted to require massive transfusion were empirically resuscitated with fresh frozen plasma and packed red blood cells in a 1:1 ratio on arrival at the combat support hospital.[73] Anecdotal success of decreased coagulopathic bleeding prompted a formal, retrospective evaluation of the strategy, which confirmed a survival benefit, and led to a dramatic change in military resuscitation and transfusion strategies.[59] Both US and British military guidelines now recommend resuscitation of severely injured personnel with equal numbers of units of red cells and plasma.[15][16][66][73] Several subsequent studies appear to confirm that these developments may be extrapolated to civilian settings.[6][60][61][63][74] The aggressive use of fresh frozen plasma remains contentious, however. While many trauma surgeons regard the available evidence as proof of effectiveness,[3][7][15][16] many haematologists disagree.[75][76] Concern has also been raised regarding the potential complications of therapy with large amounts of blood products, including the risks of major transfusion reactions, blood borne virus transmission, and transfusion-related acute lung injury.[74][76][77][78]

Key question

This section aims to answer the question "Is the early and aggressive use of fresh frozen plasma in predefined ratios with packed red blood cells associated with increased survival of trauma patients?"

Outcome measure

Survival/mortality.

Primary studies

```
Database: Ovid MEDLINE® <1950 to November Week 3 2008>
1     trauma.mp. or exp *"Wounds and Injuries"/ (505433)
2     exp *Mental Disorders/ (605325)
3     1 not 2 (491574)
4     Plasma/ (11432)
5     3 and 4 (258)
6     limit 5 to (humans and yr="1980 - 2009") (131)

Database: EMBASE <1980 to 2009 Week 05>
1      trauma.mp. or exp *"Wounds and Injuries"/ (405735)
2      exp *Mental Disorders/ (496419)
3      1 not 2 (387006)
4      Plasma/ (31849)
5      3 and 4 (475)
6      limit 5 to (human and (english or german) and yr="1980 - 2009") (259)

Inclusion criteria for abstract selection
1      Interventional or observational studies

Exclusion criteria for abstract selection
1      Case reports
2      Case series without comparison groups
```

Systematic medline and embase searches returned 390 citations. 301 titles were deemed irrelevant and excluded. Of the remaining 89 abstracts, seven met the inclusion criteria. (Fig. 5) These studies are summarised in evidence table 1.

Evidence Table 1: Primary studies

Bibliographic Citation	Study Type	Evi-dence Level	Number of Patients	Patient Charac-teristics	Intervention	Comparison	Length of Follow-Up	Outcome Measure	Effect Size
Borgman MA, et al (2007) [59]	NCCS	+	246	Military setting 94% penetrating ISS>=18 Massive transfusion (>= 10 units PRBC in 24h)	FFP:PRBC ratio	Low ratio (median 1:8) (n=31) Medium ratio (median 1:2.5) (n=53) High ratio (median 1:1.4) (n=162)	To discharge	Mortality to discharge	Low ratio group 65% Medium ratio group 34% High ratio group 19% (p<0.001)
						Low ratio (median 1:8) (n=20) Medium ratio (median 1:2.5) (n=18) High ratio (median 1:1.4) (n=31)	To discharge	Death from haemorrhage	Low ratio group 92% Medium ratio group 78% High ratio group 37% (p<0.05)
	Original and seminal study of effect of FFP:PRBC ratios. Slightly marred by vague primary outcome measure (mortality to discharge). Analysed as non-concurrent cohort study (NCCS).								

Bibliographic Citation	Study Type	Evi-dence Level	Number of Patients	Patient Charac-teristics	Intervention	Comparison	Length of Follow-Up	Outcome Measure	Effect Size
Sperry JL, et al (2008) [74]	NCCS	-	415	x7 civilian level I trauma centers 0% penetrating Hypotension (<90mmHg) Base deficit >6 meq/l Massive transfusion (>=8 U in 12 h)	FFP:PRBC ratio	Low ratio group (<1:1.5) (n=313) High ratio group (>1:1.5) (n=102)	To discharge	24h mortality	Low ratio group 13% High ratio group 4% (p=0.012)
						Low ratio group (<1:1.5) (n=313) High ratio group (>1:1.5) (n=102)		Crude mortality	Low ratio group 35% High ratio group 28% (p=0.202)
						Low ratio group (<1:1.5) (n=313) High ratio group (>1:1.5) (n=102)		PRBC transfusion requirement at 24h (mean)	Low ratio group 22U High ratio group 16U (p=0.001)
	Data obtained from another ongoing observational study. Large numbers, but statistical analysis opaque. Analysed as non-concurrent cohort study (NCCS).								
Maegele M, et al (2008) [63]	NCCS	+	713	Civilian setting ISS>16 Massive transfusion (>10 U PRBC prior to ICU admission) 7.6% penetrating	FFP:PRBC ratio	Low ratio group (<1:0.9) (n=484) Medium ratio group (1:1) (n=114) High ratio group (>1:1.1) (n=115)	To discharge	6h mortality	Low ratio group 24.6% Medium ratio group 9.6% High ratio group 3.5% (p<0.0001)
						Low ratio group (<1:0.9) (n=484) Medium ratio group (1:1) (n=114) High ratio group (>1:1.1) (n=115)		24h mortality	Low ratio group 32.6% Medium ratio group 16.7% High ratio group 11.3% (p<0.0001)
						Low ratio group (<1:0.9) (n=484) Medium ratio group (1:1) (n=114) High ratio group (>1:1.1) (n=115)		30d mortality	Low ratio group 45.5% Medium ratio group 35.1% High ratio group 24.3% (p<0.001)
	Well conducted retrospective analysis. Original paper uses PRBC:FFP (rather than FFP:PRBC) ratio, therefore converted. Analysed as non-concurrent cohort study (NCCS).								

Bibliographic Citation	Study Type	Evi-dence Level	Number of Patients	Patient Charac-teristics	Intervention	Comparison	Length of Follow-Up	Outcome Measure	Effect Size
Duchesne JC, et al (2008) [60]	NCCS 2x2	+	250	Civilian level I trauma center Average ISS 21 <= 10 units PRBC 58% penetrating	FFP:PRBC ratio	Low ratio group (<1:2) High ratio group (>1:2)	Not stated	24h Mortality	Low ratio group 21.2% High ratio group 11.8% (P=0.06)
			135	Civilian level I trauma center Average ISS 27 > 10 units PRBC 72% penetrating	FFP:PRBC ratio	Low ratio group (<1:2) High ratio group (>1:2)	Not stated	24h Mortality	Low ratio group 87.5% High ratio group 26% RR 18.88 (95% CI 6.32-56.36, p=0.001)
	2x2 factorial design incorporating analysis of patients transfused less than 10U packed red blood cells. Analysed as non-concurrent cohort study (NCCS).								
Gunter OL, et al (2008) [61]	NCCS	+	259	Civilian level I trauma center 42% penetrating Median ISS 25 Massive transfusion (>=10 U in 24 h)	FFP:PRBC ratio	Low ratio group (n=195) High ratio group (FFP:PRBC>=2:3) (n=64)	30 d	30 d Mortality	Low ratio group 62% High ratio group 41% (p=0.008)
	Well-conducted retrospective study. Analysed as non-concurrent cohort study (NCCS).								
Scalea TM, et al (2008) [79]	NCCS	-	365	12% penetrating mean ISS 29 Mean U PRBC 7.7	FFP:PRBC ratio	Low ratio group (<1:1) (n=199) High ration (1:1) (n=51)	To discharge	24 h mortality	OR 0.57 (95% CI 0.19-1.66) (p=0.34)
	Retrospective study. Methodology and statistical analysis unclear. Only 81 patients actually received massive transfusion. Analysed as non-concurrent cohort study (NCCS).								
Holcomb et al (2008) [6]	NCCS 2x2	+	466	16 US level I trauma centers Massive transfusion (>=10 units PRBC in 24 hrs) 35% penetrating 76% male Mean ISS=32 Mean age=39	FFP:PRBC ratio	Low ratio group (<1:2) (n=214) High ratio group (>1:2) (n=252)	30d	30d mortality	Low ratio group 59.6% High ratio group 40.4% (p<0.01)
	Largest and best-designed study to date. Also comprised 2x2 factorial Kaplan-Meier survival analysis incorporating effects of platelet administration. Showed statistically significant differences in mortality at 6h, 24h and 30d. (Study used survival, not mortality, as outcome measures, therefore converted.) Analysed as non-concurrent cohort study (NCCS).								

Secondary research

```
Database: MEDLINE (number of citations in brackets)
1     trauma.mp. or exp *"Wounds and Injuries"/ (505433)
2     exp *Mental Disorders/ (605325)
3     1 not 2 (491574)
4     Plasma/ (11432)
5     3 and 4 (258)
6     limit 5 to (humans and yr="1980 - 2009") (131)
7     meta-analysis/ (20263)
```

```
8     exp review literature/ (1446234)
9     (meta-analy$ or meta analy$ or metaanaly$).tw. (23776)
10    meta analysis.pt. (20263)
11    review academic.pt. (0)
12    review literature.pt. (0)
13    letter.pt. (654713)
14    review of reported cases.pt. (0)
16    review multicase.pt. (0)
17    7 or 8 or 9 or 10 or 11 or 12 (1464813)
18    13 or 14 or 15 or 16 (908067)
19    17 not 1 (1452213)
20    animal/ (4410095)
21    human/ (10826325)
22    20 and 21 (1098839)
23    20 not 22 (3311256)
24    19 not 23 (1340459)
25    4 and 24 (16)

Database: EMBASE <1980 to 2009 Week 07>
1     trauma.mp. or exp *"Wounds and Injuries"/ (406671)
2     exp *Mental Disorders/ (497727)
3     1 not 2 (387898)
4     Plasma/ (29661)
5     3 and 4 (407)
6     from 5 keep (13)

Inclusion criteria for abstract selection
1      Meta-analysis
2      Systematic review

Exclusion criteria for abstract selection
1      Non-systematic review
```

No methodologically rigorous secondary research was identified. Systematic medline searches for meta-analyses and systematic reviews returned 16 citations, and embase searches a further 13. Following review of the titles, 25 were excluded as irrelevant. (Fig. 5) The remaining four studies were found to be based on non-systematic methodology, and therefore excluded from further appraisal. Manual cross-referencing revealed numerous further non-systematic reviews, which were also excluded from further appraisal, and one systematic review of the use of fresh frozen plasma in haemorrhage in general.[80] This review was both highly heterogeneous, and contained no trauma patients, and therefore also excluded from further appraisal.

Existing guidelines

```
Database: MEDLINE (number of citations in brackets)
1     trauma.mp. or exp *"Wounds and Injuries"/ (505433)
2     exp *Mental Disorders/ (605325)
3     1 not 2 (491574)
4     Plasma/ (11432)
5     3 and 4 (258)
6     limit 5 to (humans and yr="1980 - 2009") (131)
7     guideline.pt. (14928)
8     6 and 7 (1)

Database: EMBASE <1980 to 2009 Week 07>
1     trauma.mp. or exp *"Wounds and Injuries"/ (406671)
2     exp *Mental Disorders/ (497727)
3     1 not 2 (387898)
4     exp plasma/ (31988)
5     3 and 4 (484)
```

```
6      limit 5 to human (264)
7      Practice Guideline/ (102173)
8      6 and 7 (1)

Inclusion criteria for abstract selection
1      Systematically developed guideline

Exclusion criteria for abstract selection
1      Non-systematically developed guidelines
2      Quasi-editorial guidelines
```

Systematic medline and embase searches for guidelines returned two citations, which were irrelevant and therefore excluded. Manual cross-referencing revealed numerous quasi-editorial guidelines, which were excluded, and five more formal guidelines. (Fig. 5) Two of these, on the management of massive bleeding and the use of fresh frozen plasma, cryoprecipitate and cryosupernatant, by the British Committee for Standards in Haematology, were based on a non-systematic review and published prior to most of the above-mentioned primary studies becoming available, and therefore excluded.[55][81] The third and fourth, although systematically developed, were also published before the above-mentioned primary studies became available.[57][58] The fifth, a European guideline on the management of bleeding following major trauma, was systematically developed and therefore formally appraised, and is summarised in evidence table 2.[19]

Evidence Table 2: Fresh frozen plasma (existing guidelines)

		Methodological assessment						
Biblio-graphic Citation	Summary	Scope and Purpose	Stake-holder Involve-ment	Rigour of Develop-ment	Clarity and Presen-tation	Applica-bility	Editorial Indepen-dence	Overall Assess-ment
Spahn et al (2007) [19]	This guideline recommends treatment with fresh frozen plasma in patients with massive bleeding or significant bleeding complicated by coagulopathy (defined as a PT or PTT more than 1.5x control), and accords this recommendation a GRADE 1C.	89	50	71	75	11	100	+

Diagrammatic summary of evidence selection process

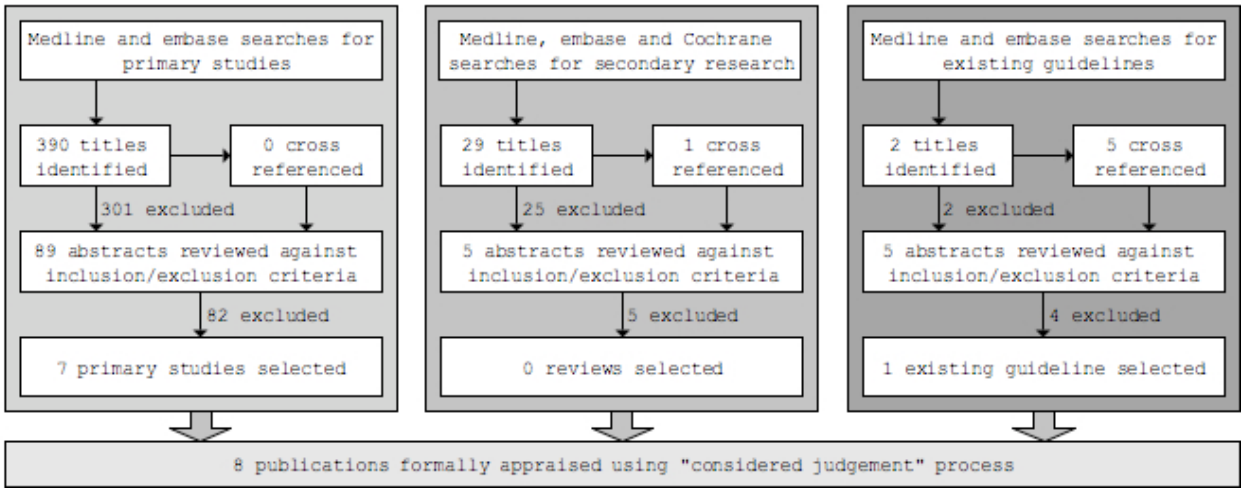

Fig 5. Diagrammatic summary of selection of literature relating to use of fresh frozen plasma.

Appraisal

Volume of evidence: The volume of evidence is moderate. All identified primary studies are retrospective database or registry analyses, which have for the purpose of this review been analysed as non-concurrent cohort studies. There is heterogeneity with regards to the definition of mortality (crude, 6 hours, 24 hours, or 30 days). There is no relevant secondary research, and only one systematically developed guideline, which is, however, of reasonable methodological quality. *Applicability:* Of the primary studies, one was conducted in the military setting, comprising almost exclusively penetrating injuries.[59] Of the remaining six studies, five were conducted in North American level I trauma centers, and one was an analysis of German trauma registry data.[6][60][61][63][74][79] Apart from Sperry's study, which contained only blunt injuries, all of the American studies contained a significant proportion of penetrating injuries, whereas the German study comprised mostly blunt trauma.[63][74] However, the pathophysiological mechanisms underlying acute traumatic coagulopathy in severely injured patients requiring massive transfusions are likely to be similar irrespective of the mechanism of injury, and these studies are therefore likely to be applicable. Only Duchesne et al investigated the effect of high ratios of FFP:PRBC in patients who received less than 10 units of packed red blood cells in the first 24 hours, and found no difference in outcome.[60] The existing guideline is aimed at general trauma patients with major haemorrhage in the setting of a European hospital, and is therefore applicable.[19] *Consistency:* Six of the seven studies showed a beneficial effect of high FFP:PRBC ratio on mortality (allowing for varying definitions, see above). One study showed no effect but was marred by poor methodology.[79] The existing guideline endorses treatment with FFP based on clinical grounds (as well as haematological abnormalities).

Evidence statements

In patients with traumatic haemorrhage predicted to require massive transfusion (defined as more than 8-10 units of packed red blood cells in the first 24 hours after injury), a high ratio of fresh frozen plasma to packed red blood cells is associated with decreased mortality.	2+
A fresh frozen plasma to packed red blood cell ratio of approximately 1:1 units appears to be optimal, although this evidence is extrapolated from studies which retrospectively stratified intervention groups for survival analysis, rather than dose-finding studies.	2+

Future research

There is an urgent need for a clinical trial of management with predetermined ratios of fresh frozen plasma to packed red blood cells versus conventional resuscitation strategies. In addition to proving efficacy, such a trial should be designed to answer what the optimal component ratio is, which patients benefit the most, how to select them, and what the risks and complications are. (These issues are discussed in more detail in section 4.1.1.)

3.2.3 Platelets

Success with the aggressive use of fresh frozen plasma in haemorrhagic shock led to a re-examination of the use of other blood products in early resuscitation. Platelets have long been recognised to play a pivotal role both in clot formation, and the regulation of the coagulation system. The administration of platelets in roughly physiological proportions compared with fresh frozen plasma and packed red blood cells was the logical next step. This strategy – known as 1:1:1 – effectively aims to reconstitute whole blood, and is thus conceptually attractive.

The term "1:1:1" refers to units of fresh frozen plasma, units of packed red blood cells, and *individual donor* units of platelets. Individual donor units of platelets are rarely used nowadays, platelets instead being issued as "pools" of 4-6 individual donor units. "1:1:1" in most European countries, where platelets are only provided in pools, therefore equates to "5 units of FFP : 5 units of PRBC : 1 *pool* of platelets".

Key question

This section aims to answer the question "Is the early and aggressive use of platelets in predefined ratios compared with packed red blood cells associated with increased survival of trauma patients?"

Outcome measure

Survival/mortality

Primary studies

```
Database: Ovid MEDLINE(R) <1950 to November Week 3 2008>
1     trauma.mp. or exp *"Wounds and Injuries"/ (505433)
2     exp *Mental Disorders/ (605325)
3     1 not 2 (491574)
4     exp Blood Platelets/  (58032)
5     3 and 4 (619)
6     limit 5 to (humans and yr="1980 - 2009") (182)

Database: EMBASE <1980 to 2009 Week 05>
1      trauma.mp. or exp *"Wounds and Injuries"/ (405735)
2      exp *Mental Disorders/ (496419)
3      1 not 2 (387006)
4      exp thrombocyte/ (28484)
```

```
5      3 and 4 (579)
6      limit 5 to (humans and yr="1980 - 2009") (290)

Inclusion criteria for abstract selection
1      Interventional or observational studies

Exclusion criteria for abstract selection
1      Case reports
2      Case series without comparison groups
```

Systematic medline and embase searches returned 472 citations. None of these publications fulfilled the inclusion criteria. (Fig. 6) Manual cross-referencing revealed two relevant published studies,[6][61] which analysed the effect of aggressive platelet administration in addition to liberal fresh frozen plasma use, and are summarised in evidence table 3.

Evidence Table 3: Primary studies

Bibliographic Citation	Study Type	Evi-dence Level	Number of Patients	Patient Charac-teristics	Intervention	Comparison	Length of Follow-Up	Outcome Measure	Effect Size
Holcomb et al (2008) [6]	NCCS 2x2	+	466	16 US level I trauma centers Massive transfusion (>=10 units PRBC in 24 hrs) 35% penetrating 76% male Mean ISS=32 Mean age=39	PLT:PRBC ratio	Low ratio group (<1:2) (n=232) High ratio group (>1:2) (n=233)	30d	30d survival	Low ratio group 40.1% High ratio group 59.9% (P<0.01)
	Also comprised 2x2 factorial Kaplan-Meier survival analysis incorporating effect of platelet administration. Showed statistically significant differences in survival at 6h, 24h and 30d.								
Gunter OL, et al. (2008) [61]	NCCS	+	259	Civilian level I trauma center 42% penetrating Median ISS 25 Massive transfusion (>=10 U in 24 h)	PLT:PRBC ratio	Low ratio group (n=195) High ratio group (PLT:PRBC>=1:5) (n=66)	30 d	30 d Mortality	Low ratio group 61% High ratio group 38% P=0.001
	Well-conducted retrospective study. Analysed as non-concurrent cohort study (NCCS).								

Secondary research

```
Database: Ovid MEDLINE(R) <1950 to November Week 3 2008>
1      trauma.mp. or exp *"Wounds and Injuries"/ (505433)
2      exp *Mental Disorders/ (605325)
3      1 not 2 (491574)
4      exp Blood Platelets/ (59724)
5      3 and 4 (619)
6      meta-analysis/ (20263)
7      exp review literature/ (1446234)
8      (meta-analy$ or meta analy$ or metaanaly$).tw. (23776)
9      meta analysis.pt. (20263)
10     review academic.pt. (0)
11     review literature.pt. (0)
12     letter.pt. (654713)
13     review of reported cases.pt. (0)
14     historical article.pt. (258893)
```

```
15    review multicase.pt. (0)
16    6 or 7 or 8 or 9 or 10 or 11 (1464813)
17    12 or 13 or 14 or 15 (908067)
18    16 not 17 (1452213)
19    animal/ (4410095)
20    human/ (10826325)
21    19 and 20 (1098839)
22    19 not 21 (3311256)
23    18 not 22 (1340459)
24    5 and 23 (64)

Database: EMBASE <1980 to 2009 Week 07>
1     trauma.mp. or exp *"Wounds and Injuries"/ (406671)
2     exp *Mental Disorders/ (497727)
3     1 not 2 (387898)
4     Thrombocyte/ (26432)
5     3 and 4 (566)
6     limit 5 to (human and english) (251)
7     limit 5 to (human and german) (13)
8     6 or 7 (264)
9     from 8 keep (79)

Inclusion criteria for abstract selection
1     Systematic reviews
2     Meta-analyses

Exclusion criteria for abstract selection
1     Non-systematic reviews
2     Quasi-editorial guidelines
```

No methodologically rigorous secondary research was identified. Systematic medline searches for meta-analyses and systematic reviews returned 64 citations, and embase searches a further 79. Following review of the abstracts, 141 were excluded as irrelevant. The remaining two were found to be based on non-systematic methodology, and therefore excluded from further appraisal.[51][73] (Fig. 6) Manual cross-referencing revealed numerous non-systematic reviews, which were excluded from further analysis.

Existing guidelines

```
Database: Ovid MEDLINE(R) <1950 to November Week 3 2008>
1     trauma.mp. or exp *"Wounds and Injuries"/ (505433)
2     exp *Mental Disorders/ (605325)
3     1 not 2 (491574)
4     exp Blood Platelets/ (59724)
5     3 and 4 (619)
6     guideline.pt. (14928)
7     5 and 6 (0)

Database: EMBASE <1980 to 2009 Week 01>
1     trauma.mp. or exp *"Wounds and Injuries"/ (404150)
2     exp *Mental Disorders/ (494289)
3     1 not 2 (385487)
4     exp Thrombocyte/ (28489)
5     guideline.mp. (105785)
6     4 and 5 (85)
7     limit 6 to (human and (english or german) and yr="1980 - 2009") (68)
8     from 7 keep (0)
```

```
Inclusion criteria for abstract selection
1      Guidelines

Exclusion criteria for abstract selection
1      Quasi-editorial guidelines
```

Systematic medline and embase searches for guidelines returned no citations. Manual cross-referencing revealed numerous quasi-editorial guidelines, which were excluded from further analysis. Two more formal guidelines, which have been mentioned previously, also make recommendations regarding the use of platelets in trauma. (Fig. 6) The British Committee for Standards in Haematology guideline on the management of massive bleeding was, however, based on a non-systematic review and published prior to the above-mentioned primary studies becoming available, and therefore excluded.[55] The European guideline on the management of bleeding following major trauma, which was appraised in section 3.2.2, only makes reference to the administration of platelets in response to thrombocytopaenia, and was therefore also excluded.[19]

DIAGRAMMATIC SUMMARY OF EVIDENCE SELECTION PROCESS

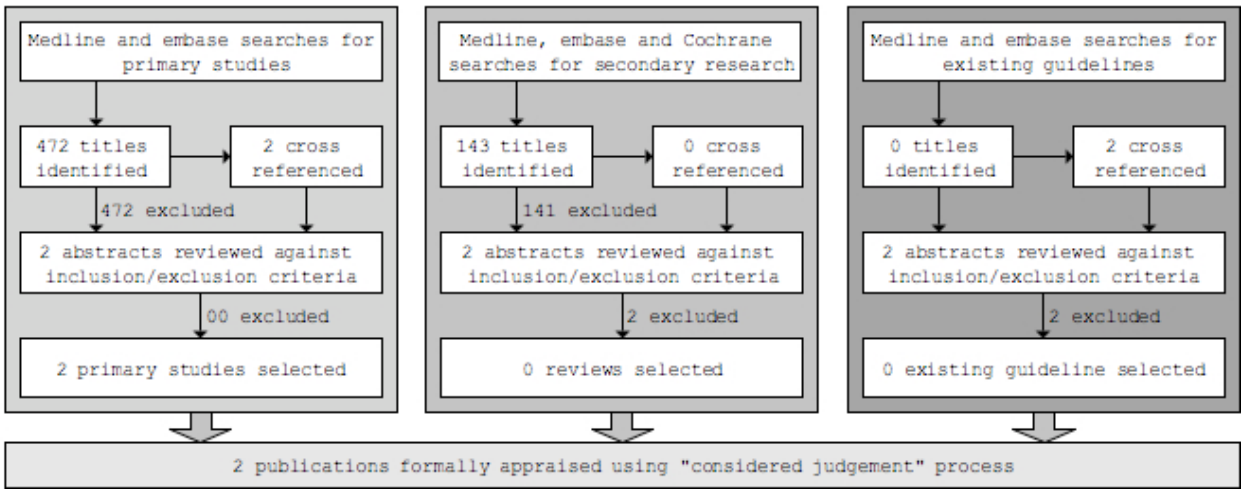

Fig 6. Diagrammatic summary of selection of literature relating to platelet use

Appraisal

Volume of evidence: The volume of evidence is poor. The two primary studies, both of which also investigated the effect of fresh frozen plasma (see section 3.2.2), are retrospective database trawls, and are thus prone to confounding.[6][61] There are no systematic reviews, and no applicable existing guidelines. *Applicability:* The available primary studies are applicable to the guideline's target population. *Consistency:* The limited results available are consistent.

Evidence statements

In patients with traumatic haemorrhage predicted to require massive transfusion (defined as more than 8-10 units of packed red blood cells in the first 24 hours after injury), a high ratio of units of platelets to packed red blood cells is associated with decreased mortality. A ratio of at least 1 (pooled) unit of platelets to 5 units of packed red blood cells appears to be optimal, although this evidence is extrapolated from studies which retrospectively stratified intervention groups for survival analysis.	2-

Future research

Although consistent, the current volume of evidence supporting the liberal use of platelets is poor. In addition to the already mentioned need for a trial of fresh frozen plasma to packed red blood cell ratios, there is also a need for a trial of different platelet to packed red blood cell ratios, and administration regimes. These studies could be combined.

3.2.4 Recombinant factor VIIa

Recognition of the importance of traumatic coagulopathy has also prompted a search for pharmacological adjuncts to treatment. Recombinant activated factor VIIa (RFVIIa; eptacog ∝-activated; Novoseven®, Novo Nordisk®, Crawley, Surrey, UK) was introduced into clinical practice in the 1980s for the treatment of haemophiliacs with inhibitory antibodies to factor VIII and IX, but has since been used widely for the treatment of patients with acquired coagulopathy.[82]

Factor VII is an important initial component of the coagulation cascade, and acts via two linked pathways to produce thrombin.[82] The first involves the binding of factor VIIa to subendothelial tissue factor exposed by vessel injury. This reaction in turn activates factor X, resulting in the generation of a small amount of thrombin (factor IIa). Thrombin then activates platelets and factors V and VIII. Activated platelets also bind circulating factor VIIa – the second pathway – resulting in further factor Xa generation, as well as activation of factor IX. IXa (with its cofactor VIIIa) yields additional Xa. The complex of Xa and its cofactor Va then converts prothrombin into thrombin in amounts that are sufficient to induce the conversion of fibrinogen to fibrin (“thrombin burst”). [83]

Recombinant factor VIIa is manufactured using recombinant DNA technology. The amino acid sequence is identical to the human plasma protein, but there are minor differences in post-translational changes.[82] Recombinant factor VIIa has a half-life of 2-3 hours, less in bleeding

patients and children.[82] In vitro studies show the activity of rFVIIa to be markedly affected by acidaemia: A decrease from pH 7.4 to 7.0 decreases the activity of FVIIa on platelets by 90%, and FVIIa/TF by 60%. In contrast, a reduction in temperature from 37°C to 33°C did not decrease FVIIa activity on platelets, and reduced the FVIIa/TF activity by only 20%.[82]

Randomised studies support the use of recombinant activated factor VIIa in open prostatectomy, intracranial bleeding, cardiac surgery, upper gastrointestinal haemorrhage and hepatic resection, and the rationale for investigating its use in traumatic bleeding is self-evident.[82][84] Dramatic early reports of successful treatment of otherwise hopeless post-traumatic bleeding prompted increased off-licence use of rFVIIa for trauma patients.[85][86][87][88][89][90][91] Several subsequent case series, retrospective analyses, and registry reviews have confirmed the safety of factor VIIa use in trauma, but are highly heterogeneous, and owing to the lack of a control group, cannot prove effectiveness.[92][93][94][95][96][97][98] These studies have therefore been excluded from this analysis. In contrast to many other areas of trauma management, the use of rFVIIa has, however, been subjected to randomised trials.

The dosing of recombinant factor VIIa remains contentious, although the majority of recent studies have adopted the regime used in the two randomised controlled trials, consisting of an initial 200 mcg/kg bolus followed by two further doses of 100 mcg/kg if haemorrhage persists.[99] Although in general a safe drug, recombinant factor VIIa may be associated with a trend towards thromboembolic complications.[100]

Key question

This section aims to answer the questions “Does factor VIIa improve survival in trauma patients with severe bleeding?” and “Does factor VIIa reduce transfusion requirements in trauma patients?”.

Outcome measures

Mortality/survival and transfusion requirements.

Primary studies

```
Database: Ovid MEDLINE(R) <1950 to November Week 3 2008>
1     trauma.mp. or exp *"Wounds and Injuries"/ (505433)
2     exp *Mental Disorders/ (605325)
3     1 not 2 (491574)
4     exp Factor VIIa/ (1843)
5     3 and 4 (128)
6     limit 5 to (humans and yr="1980 - 2009" and (english or german)) (114)
```

```
Database: EMBASE <1980 to 2009 Week 01>
1     trauma.mp. or exp *"Wounds and Injuries"/ (404150)
2     exp *Mental Disorders/ (494289)
3     1 not 2 (385487)
4     exp Blood Clotting Factor 7a/ (1480)
5     3 and 4 (66)
6     limit 5 to (human and yr="1980 - 2009") (52)

Inclusion criteria for abstract selection
1      Interventional studies
2      Observational studies

Exclusion criteria for abstract selection
1      Case reports
2      Case series without comparison groups
```

Systematic searches across medline and embase returned 166 citations. Following review of the abstracts, 162 were excluded as irrelevant or not meeting the above inclusion criteria, leaving four studies which were appraised in full. One was subsequently excluded as the authors had failed to fulfill the methodology described in the abstract.[92] One of the remaining three studies consisted of two parallel trials, which have been analysed as such. (Fig. 7) These studies are summaries in evidence table 4.

Evidence table 4: Recombinant factor VIIa (primary studies)

Bibliographic Citation	Study Type	Evi-dence Level	Number of Patients	Patient Charac-teristics	Intervention	Comparison	Length of Follow-Up	Outcome Measure	Effect Size
Spinella PC et al (2008) [101]	NCCS	+	124	Military ISS>15 Massive transfusion >=10U/24h 92% penetrating	RFVIIa	RFVIIa (n=49) vs no RFVIIa (n=75)	30d	24h mortality	RFVIIa- (26/75) 35% RFVIIa+ (7/49) 14% (p=0.01)
						RFVIIa (n=49) vs no RFVIIa (n=75)	30d	30d mortality	RFVIIa- (38/75) 51% RFVIIa+ (15/49) 31% (p=0.03)
						RFVIIa (n=14) vs no RFVIIa (n=37)	30d	Death from haemorrhage	RFVIIa- (29/37) 78% RFVIIa+ (8/14) 57% (p=0.12)
	Retrospective study with significant potential confounders. Virtually all military ballistic injuries treated in Combat Support Hospital, hence not directly applicable to civilian setting.								

Bibliographic Citation	Study Type	Evi-dence Level	Number of Patients	Patient Charac-teristics	Intervention	Comparison	Length of Follow-Up	Outcome Measure	Effect Size
Boffard KD et al (2005) [99]	RCT	+	143	Civilian Multicentre ISS>15 Massive transfusion >=6 in 4h Blunt trauma	RFVIIa	Placebo (n=74) vs RFVIIa (n=69)	30d	Decrease in 48h transfusion requirement	2.6U (90% CI 0.7-4.6) (p=0.02)
								48h mortality	Placebo 18% VIIa 19% (p=1.00)
								30d mortality	Placebo 30% VIIa 25% (p=0.58)
	Complex, parallel studies with some methodological issues, but only RCTs to date. Powered to detect difference in transfusion requirements, not mortality. Timing of administration of VIIa (after transfusion of 8U PRBC) may have been too late. Other treatment (surgical and non-surgical) not standardised. High proportion of patients lost to follow-up. Statistical analysis opaque.								
Boffard KD et al (2005) [99]	RCT	+	134	Civilian Multicentre ISS>15 Massive transfusion >=6 in 4h Penetrating trauma	RFVIIa	Placebo (n=64) vs RFVIIa (n=70)	30d	Decrease in 48h transfusion requirement	1.0U (90% CI 0.0-4.6) (p=0.1)
								48h mortality	Placebo 16% VIIa 17% (p=1.00)
								30d mortality	Placebo 28% VIIa vs 24% (p=0.69)
	Complex, parallel studies with some methodological issues, but only RCTs to date. Powered to detect difference in transfusion requirements, not mortality. Timing of administration of VIIa (after transfusion of 8U PRBC) may have been too late. Other treatment (surgical and non-surgical) not standardised. High proportion of patients lost to follow-up. Statistical analysis opaque.								
Rizoli S et al (2006) [102]	NCCS	-	240	Civilian Multicentre Mean ISS 30 (coagulo-pathic group), 24 (non-coagulopathic group) Mean 8.4U PRBC before intervention	RFVIIa	Coagulo-pathic patients (n=136) vs non-coagulopathic patients (n=104)	30d	48h mortality (although only stated in baseline charac-teristics)	Coag gp 15% Non-coag gp 19% (p=0.44)
								30d mortality (although only stated in baseline charac-teristics)	Coag gp 24% Non-coag gp 28% (p=0.44)
								48h PRBC requirement	Decreased by 2.6 units (p=0.02)
	Poor quality post-hoc subgroup analysis of data from Boffard randomised controlled trial (see above), comparing coagulopathic with non-coagulopathic patients (retrospectively defined by blood products administered). Main problem relates to identification of coagulopathic and non-coagulopathic patients on basis of blood products administered. Mortality only described in baseline characteristics table, rather than as outcome measure. Actual outcome measures are surrogate markers.								

Secondary research

```
Database: Ovid MEDLINE(R) <1950 to November Week 3 2008>
1     trauma.mp. or exp *"Wounds and Injuries"/ (505433)
2     meta-analysis/ (20263)
3     exp review literature/ (1446234)
4     (meta-analy$ or meta analy$ or metaanaly$).tw. (23776)
5     meta analysis.pt. (20263)
6     review academic.pt. (0)
7     review literature.pt. (0)
8     letter.pt. (654713)
9     review of reported cases.pt. (0)
10    historical article.pt. (258893)
11    review multicase.pt. (0)
12    2 or 3 or 4 or 5 or 6 or 7 (1464813)
13    8 or 9 or 10 or 11 (908067)
14    12 not 13 (1452213)
15    animal/ (4410095)
16    human/ (10826325)
17    15 and 16 (1098839)
18    15 not 17 (3311256)
19    14 not 18 (1340459)
20    exp *Mental Disorders/ (605325)
21    1 not 20 (491574)
22    exp Factor VIIa/ (1843)
23    21 and 22 (128)
24    (brain or intracerebral or extradural or subdural).m_titl. (208677)
25    23 not 24 (116)
26    limit 25 to (humans and yr="1980 - 2009" and (english or german)) (102)
27    26 and 19 (27)

Database: EMBASE <1980 to 2009 Week 07>
1     trauma.mp. or exp *"Wounds and Injuries"/ (406671)
2     exp *Mental Disorders/ (497727)
3     1 not 2 (387898)
4     Blood Clotting Factor 7a/ (1492)
5     "Review"/ (931130)
6     3 and 4 (68)
7     5 and 6 (17)
8     from 7 keep 1-10 (10)

Inclusion criteria for abstract selection
1      Systematic reviews
2      Meta-analyses

Exclusion criteria for abstract selection
1      Non-systematic reviews
```

Systematic searches for meta-analyses and systematic reviews using the NHS Centre for Reviews and Dissemination's filter, which is only available for medline, returned 27 citations, and embase searches a further 10. Following review of the abstracts, all were found to be based on non-systematic methodology, and therefore excluded from further appraisal. A search of the Cochrane Database revealed one systematic review, appraised in evidence table 5. Manual cross-referencing revealed numerous further non-systematic reviews, which were excluded from further analysis. (Fig. 7)

Evidence Table 5: Recombinant factor VIIa (secondary research)								
Bibliographic Citation	Study Type	Evi-dence Level	Number of Patients	Primary studies included	Intervention	Comparison	Outcome Measure	Effect Size
Stanworth et al (2007) [100]	CSR	+	1214	7 RCTs (only 2 pertaining to trauma) examining therapeutic use of rFVIIa in a variety of settings (incl. non-trauma)	RFVIIa	RFVIIa vs placebo	Mortality (not further defined)	RR 0.82 (95% CI 0.64 to 1.04)
				4 RCTs (but only 2 pertaining to trauma) examining therapeutic use of rFVIIa in a variety of settings (incl. non-trauma)	RFVIIa	RFVIIa vs placebo	Red cell transfusion requirement	Weighted Mean Difference (WMD) 56mL (95% CI -148 to 260)
	This Cochrane Review was heterogeneous and has only limited applicability. Of 13 included placebo-controlled trials, six related to the prophylactic use of rFVIIa. Seven trials examined the effect of rFVIIa in a therapeutic role, but only two pertained to trauma (Boffard et al). Pooled outcomes did not show evidence of an advantage of rFVIIa over placebo, although there was a trend in favour of rFVIIa treatment for mortality.							

Existing guidelines

```
Database: Ovid MEDLINE(R) <1950 to November Week 3 2008>
1      guideline.pt. (14928)
2      trauma.mp. or exp *"Wounds and Injuries"/ (505433)
3      exp *Mental Disorders/ (605325)
4      2 not 3 (491574)
5      exp Factor VIIa/ (1843)
6      4 and 5 (128)
7      (brain or intracerebral or extradural or subdural).m_titl. (208677)
8      6 not 7 (116)
9      limit 8 to (humans and yr="1980 - 2009" and (english or german)) (102)
10     8 and 1 (0)

Database: EMBASE <1980 to 2009 Week 02>
1      trauma.mp. or exp *"Wounds and Injuries"/ (404584)
2      exp *Mental Disorders/ (494775)
3      1 not 2 (385908)
4      exp Blood Clotting Factor 7a/ (1482)
5      3 and 4 (66)
6      (guideline or guidance).mp. [mp=title, abstract, subject headings, heading
       word, drug trade name, original title, device manufacturer, drug manufacturer
       name] (131903)
7     5 and 6 (0)

Inclusion criteria for abstract selection
1      Guidelines

Exclusion criteria for abstract selection
1      Quasi-editorial guidelines
```

Systematic medline and embase searches for guidelines returned one citation.[104] Manual cross-referencing identified three further guidelines.[19][55][103] (Fig. 7) Two of these were published prior to the reporting of the above-mentioned randomised trials, and therefore regarded as superseded and excluded.[55][103]

Evidence Table 6: Recombinant factor VIIa (existing guidelines)								
		Methodological assessment						
Biblio-graphic Citation	Summary	Scope and Purpose	Stake-holder Involve-ment	Rigour of Develop-ment	Clarity and Presen-tation	Applica-bility	Editorial Indepen-dence	Overall Assess-ment
Hodgetts et al (2007b) [104]	This guideline addresses the use of rFVIIa in the military setting. It recommends rFVIIa administration for life-threatening haemorrhage (defined as loss of entire blood volume within 24h, loss of 50% of blood volume within 3h, blood loss at a rate of 150ml/m, blood loss at a rate of 1.5 ml/kg/min for 20 min or more), when conventional resuscitation and/or surgical techniques have failed.	100	25	10	50	33	100	+
Spahn et al (2007) [19]	This guideline is intended for civilian use. It recommends administration of RFVIIa in blunt trauma, if major bleeding persists despite standard measures, and best-practice use of blood components. This recommendation is accorded a GRADE of 2C.	89	50	71	75	11	100	+

Diagrammatic summary of evidence selection process

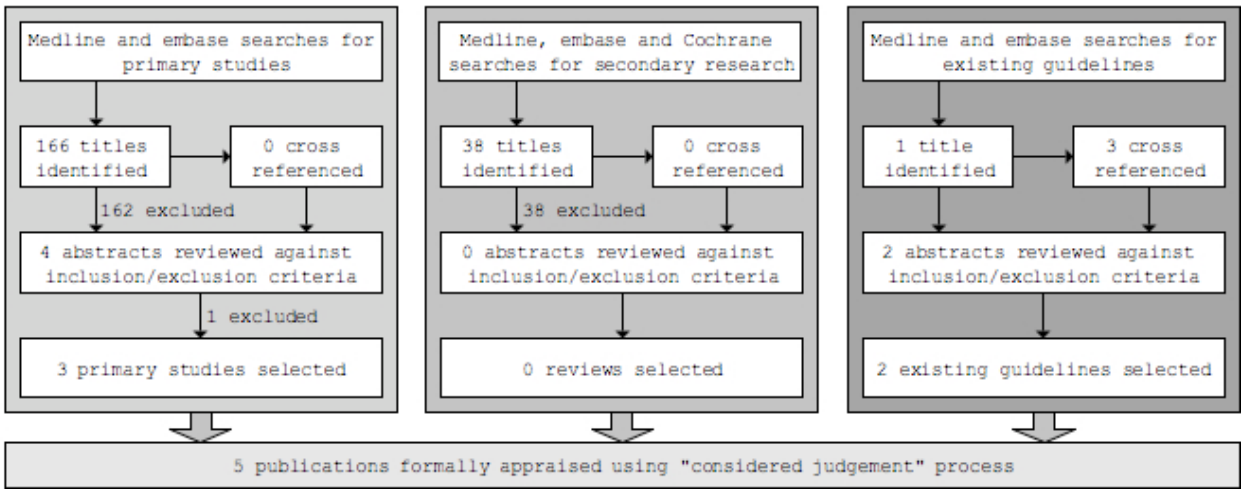

Fig 7. Diagrammatic summary of selection of literature relating to platelet use

Appraisal

Volume of evidence: There is a large volume of low and very low quality evidence, principally consisting of anecdotal reports and small, uncontrolled case series. These publications have been excluded from this appraisal. The use of recombinant factor VIIa is, however, also one of the few areas in trauma care to have been subjected to randomised controlled trials, but these studies were marred by methodological problems.[99] The recruitment of suitable participants necessitated a multi-national, multi-centre design, reflecting the complexity and effort required to study the effects of an intervention in emergency patients. Other than the administration of rFVIIa, treatment – and the administration of other blood products such as FFP in particular – was not standardised. Several authorities have argued that the first dose of rFVIIa given after 8 units of transfused packed red blood cells may have been "too little, too late. Concealment of allocation was unclear, a substantial proportion of patients were lost to follow-up, and the

statistical analysis was opaque. Despite these limitations, these trials are important. Although there was no difference in mortality (which the trials were never powered to detect), factor VIIa reduced blood transfusion requirements in patients with blunt trauma. Other than the two parallel trials conducted by Boffard et al, there is only one small non-concurrent cohort study of the effect of rFVIIa, in military patients. Existing systematic reviews and guidelines reflect the paucity of evidence and rely heavily on the results of the paired trials. *Applicability:* Other than the small retrospective study of rFVIIa in military patients, the studies, reviews and guidelines included are applicable to this guideline's target population. However, all of these studies were conducted before the aggressive use of fresh frozen plasma in trauma resuscitation became commonplace. The place of rFVIIa in this setting is thus difficult to ascertain. *Consistency:* The volume of evidence is too small to comment on consistency.

Evidence statements

Recombinant factor VIIa reduces transfusion needs in blunt trauma patients requiring massive transfusion (defined as more than 8 units of packed red blood cells). The effect of recombinant factor VIIa on mortality/survival in this setting is not known.	1-
Recombinant factor VIIa may also reduce transfusion needs in penetrating trauma patients requiring massive transfusion (defined as more than 8 units of packed red blood cells), but the evidence in this setting is less clear. As in blunt trauma, the effect of recombinant factor VIIa on mortality/survival in this setting is also not known.	1-

Future Research

All studies of rFVIIa, including the two trials on which these recommendations are based, were conducted prior to the acceptance of aggressive fresh frozen plasma therapy as the standard of care, and it is conceivable that the earlier use of such blood products will lead to a decreased need for rFVIIa. Given the substantial cost of this intervention, further studies are needed to define the place of recombinant factor VIIa in haemostatic resuscitation.

3.2.5 Cryoprecipitate

Fibrinogen deficiency develops earlier than any other clotting factor deficiency following major haemorrhage, and the use of cryoprecipitate, which contains factor VIII, factor XIII, von Willebrand factor (vWF) and fibrinogen, is therefore conceptually attractive.[66][105][106][107] In addition to replacing deficient fibrinogen, the vWF contained in cryoprecipitate may enhance platelet aggregation and adhesion.[51] Although current transfusion strategies with high ratios of

FFP and platelets seem very successful, several authorities have suggested that the role of cryoprecipitate in coagulopathic trauma patients should be re-evaluated.[51][66] The use of cryoprecipitate is tempered by concerns about patient exposure to large numbers of donors, and associated risks of blood borne virus transmission.

Key question

This section aims to answer the question "Does the use of cryoprecipitate improve survival in trauma patients?"

Outcome measures

Mortality/survival

Primary Studies

```
Database: Ovid MEDLINE(R) <1950 to February Week 2 2009>
1     trauma.mp. or exp *"Wounds and Injuries"/ (488200)
2     exp *Mental Disorders/ (582078)
3     1 not 2 (474751)
4     cryoprecipitate.mp. (1401)
5     3 and 4 (66)
6     limit 5 to (humans and yr="1980 - 2009" and (english or german)) (49)
7     from 6 keep 2-6 (5)

Database: EMBASE <1980 to 2009 Week 07>
1     trauma.mp. or exp *"Wounds and Injuries"/ (406671)
2     exp *Mental Disorders/ (497727)
3     1 not 2 (387898)
4     *Cryoprecipitate/ (237)
5     3 and 4 (7)
6     from 5 keep (0)

Inclusion criteria for abstract selection
1      Interventional studies
2      Observational studies

Exclusion criteria for abstract selection
1      Case reports
2      Case series without comparison groups
```

Systematic medline and embase searches returned 56 citations, of which 51 were excluded as irrelevant following title review. Of the remaining 5 abstracts, only one was found to meet the inclusion criteria.[108] (Fig. 8)

Evidence Table 7: Cryoprecipitate (primary studies)

Bibliographic Citation	Study Type	Evi-dence Level	Number of Patients	Patient Charac-teristics	Intervention	Comparison	Length of Follow-Up	Outcome Measure	Effect Size
Stinger et al (2008) [108]	NCCS	-	252	Military setting Mean ISS 21	Fibrinogen administration	Low fib: PRBC ratio (<0.2g/U) (n=52) High fib: PRBC ratio (>0.2g/U) (n=200)	To discharge	Survival	Low gp 52% High gp 24% (p<0.001) OR of death 0.37 (95%CI 0.171-0.812, p=0.013)
	Database study of calculated amount of fibrinogen administered (in FFP, platelets, whole blood, PRBCs, or as cryoprecipitate). Retrospective design and assumptions regarding fibrinogen content of the products used make the validity of the conclusions questionable.								

Secondary research

```
Database: Ovid MEDLINE(R) <1950 to February Week 2 2009>
1      trauma.mp. or exp *"Wounds and Injuries"/ (488200)
2      exp *Mental Disorders/ (582078)
3      1 not 2 (474751)
4      cryoprecipitate.mp. (1401)
5      3 and 4 (66)
6      limit 5 to (humans and yr="1980 - 2009" and (english or german)) (49)
7      meta-analysis/ (19931)
8      exp review literature/ (1416721)
9      (meta-analy$ or meta analy$ or metaanaly$).tw. (23482)
10     meta analysis.pt. (19931)
11     review academic.pt. (0)
12     review literature.pt. (0)
13     letter.pt. (638576)
14     review of reported cases.pt. (0)
15     historical article.pt. (251498)
16     review multicase.pt. (0)
17     7 or 8 or 9 or 10 or 11 or 12 (1434959)
18     13 or 14 or 15 or 16 (884681)
19     17 not 18 (1422622)
20     animal/ (4310239)
21     human/ (10508643)
22     20 and 21 (1074690)
23     20 not 22 (3235549)
24     19 not 23 (1312678)
25     6 and 24 (9)
26     from 25 keep 1-5 (5)

Database: EMBASE <1980 to 2009 Week 07>
1      trauma.mp. or exp *"Wounds and Injuries"/ (406671)
2      exp *Mental Disorders/ (497727)
3      1 not 2 (387898)
4      *Cryoprecipitate/ (237)
5      3 and 4 (7)
6      from 5 keep (0)

Inclusion criteria for abstract selection
1      Systematic reviews
2      Meta-analyses

Exclusion criteria for abstract selection
1      Non-systematic reviews
```

No methodologically rigorous secondary research was identified. Systematic medline, embase, and Cochrane library searches returned 16 citations. 11 were excluded as irrelevant on title review. Of the remaining 5 review articles, none were based on systematic methodology, and therefore excluded from further appraisal. (Fig.8)

Existing guidelines

```
Database: Ovid MEDLINE(R) <1950 to February Week 2 2009>
1      trauma.mp. or exp *"Wounds and Injuries"/ (488200)
2      exp *Mental Disorders/ (582078)
3      1 not 2 (474751)
4      cryoprecipitate.mp. (1401)
5      3 and 4 (66)
6      limit 5 to (humans and yr="1980 - 2009" and (english or german)) (49)
7      guideline.pt. (0)

Database: EMBASE <1980 to 2009 Week 07>
1      trauma.mp. or exp *"Wounds and Injuries"/ (406671)
2      exp *Mental Disorders/ (497727)
```

```
3      1 not 2 (387898)
4      *Cryoprecipitate/ (237)
5      3 and 4 (7)
6      from 5 keep (0)

Inclusion criteria for abstract selection
1      Guidelines

Exclusion criteria for abstract selection
1      Quasi-editorial guidelines
```

Systematic medline and embase searches for existing guidelines returned no citations. Manual cross-referencing, however, revealed four relevant articles.[19][55][56][81] (Fig.8)

Evidence Table 8: Cryoprecipitate (existing guidelines)

		Methodological assessment						
Biblio-graphic Citation	Summary	Scope and Purpose	Stake-holder Involve-ment	Rigour of Develop-ment	Clarity and Presen-tation	Applica-bility	Editorial Indepen-dence	Overall Assess-ment
Spahn et al (2007) [19]	This guideline recommends "treatment with fibrinogen concentrate or cryoprecipitate if significant bleeding is accompanied by a plasma fibrinogen level of less than 1.0 g/l." It accords this recommendation a GRADE 1C.	89	50	71	75	11	100	+
Stainsby et al (2006) [55]	This guideline, which is not specifically aimed at trauma patients, recommends that cryoprecipitate therapy should be considered if fibrinogen levels remain low (<1.0g/l) despite fresh frozen plasma administration. This recommendation is based on a guideline issued by the College of American Pathologists (Lundberg 1994).	78	25	38	50	44	100	+
Lundberg (1994) [56]	This guideline, not specifically aimed at trauma patients, recommends cryoprecipitate for the correction of fibrinogen deficits refractory to therapy with fresh frozen plasma (<1.0g/l). This document is included for completeness, as it is still often quoted. The methodology used to derive the recommendations is unclear.	33	25	9	25	0	10	-
O'Shaughn essy et al (2004) [81]	This guideline states that cryoprecipitate should be given so that a fibrinogen concentration of at least 1.0 g/l is obtained.	67	25	14	25	11	67	-

Diagrammatic summary of evidence selection process

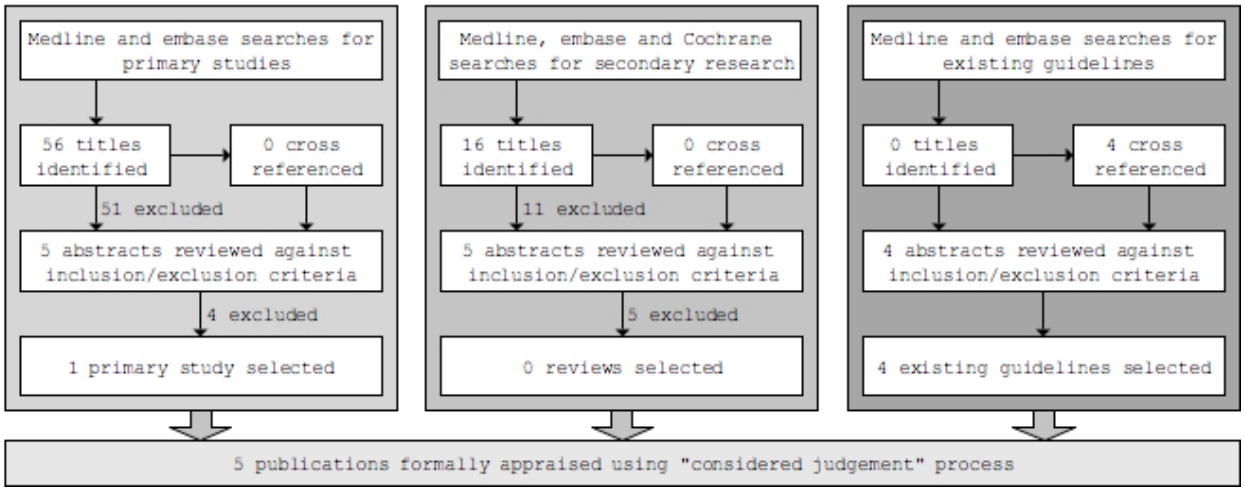

Fig 8. Diagrammatic summary of selection of literature relating to use of cryoprecipitate

Appraisal

Volume of evidence: The volume of evidence for the use of cryoprecipitate in traumatic haemorrhage is poor. Only one poor quality primary study was identified.[108] This study retrospectively compared outcome with the calculated amount of fibrinogen administered, in various forms, and is therefore liable to significant confounding.[108] Current guidelines, many of which are not specifically aimed at trauma patients, are based on observational and extrapolated data. The European guideline for the management of bleeding following major trauma is based on satisfactory methodology, but the British committee for standards in haematology guideline merely reiterates guidance published by College of American Pathologists in 1994 and is therefore outdated.[19][55][56] *Applicability:* The only primary study was conducted in military patients, and may thus not be relevant to civilian practice. *Consistency:* As there is only one study, consistency could not be assessed.

Evidence statement

The use of cryoprecipitate in exsanguinating haemorrhage is founded on reasonable scientific principles, but its use in trauma patients is largely based on studies of poor methodology, and extrapolated data. Cryoprecipitate should be considered when hypofibrinogenaemia has been confirmed, or when traumatic coagulopathy, whether diagnosed clinically or by assay, is not responding to other methods of haemostatic resuscitation.	3

Future research

There is a need to better define the role of cryoprecipitate, and other single-factor concentrates (such as fibrinogen) and complexes (such as prothrombin complex concentrate), in the management of traumatic coagulopathy.

3.2.6 Tranexamic acid

Antifibrinolytics such as tranexamic acid, aprotinin, and aminocaproic acid have been shown to reduce blood loss after elective – particularly cardiac and liver transplantation – surgery.[109] [110][111][112] Recognition of the contribution of hyperfibrinolysis to the development of the acute coagulopathy of trauma shock has led to renewed interest in their use in trauma patients.[113] Tranexamic acid and aminocaproic acid are lysine analogues which stabilise clot by competitively inhibiting lysine binding sites of the plasminogen molecule, preventing complexation with t-PA and fibrin, and inhibiting fibrinolysis.[112] Aprotinin is a broadspectrum serine protease inhibitor. Aminocaproic acid and aprotinin are not available in the

UK, the licence for the latter having been withdrawn following reports of increased cardiovascular and renal complications following coronary artery bypass grafting.[114] Tranexamic acid is therefore the only readily available antifibrinolytic agent.

Key question

This section aims to answer the question "Does tranexamic acid reduce transfusion requirements and/or mortality in trauma patients?"

Outcome measures

Blood loss, mortality/survival.

Primary Studies

```
Database: Ovid MEDLINE(R) <1950 to January Week 3 2009>
1      trauma.mp. or exp *"Wounds and Injuries"/ (486169)
2      exp *Mental Disorders/ (580167)
3      1 not 2 (472776)
4      Tranexamic Acid/ (1277)
5      3 and 4 (52)
6      limit 5 to yr="1980 - 2009" (42)
7      limit 6 to (english or german) (36)
8      from 7 keep 0

Database: EMBASE <1980 to 2009 Week 05>
1      trauma.mp. or exp *"Wounds and Injuries"/ (405735)
2      exp *Mental Disorders/ (496419)
3      1 not 2 (387006)
4      Tranexamic Acid/ (3385)
5      3 and 4 (212)
6      limit 5 to (human and (english or german) and yr="1980 - 2009") (151)
7      from 6 keep 0

Inclusion criteria for abstract selection
1      Interventional studies
2      Observational studies

Exclusion criteria for abstract selection
1      Case reports
2      Case series without comparison groups
```

Systematic searches of the medline and embase databases returned no completed primary studies of tranexamic acid in trauma patients. (Fig. 9) The two trials included in the Cochrane review on antifibrinolytic drugs for acute traumatic injury both trialled aprotinin rather than tranexamic acid.[115] In addition, these studies were small, outdated, and of questionable methodology.

Secondary research

```
Database: Ovid MEDLINE(R) <1950 to January Week 3 2009>
1      trauma.mp. or exp *"Wounds and Injuries"/ (486169)
2      exp *Mental Disorders/ (580167)
3      1 not 2 (472776)
4      Tranexamic Acid/ (1277)
5      3 and 4 (52)
6      limit 5 to yr="1980 - 2009" (42)
7      limit 6 to (english or german) (36)
8      meta-analysis/ (19624)
9      exp review literature/ (1406546)
```

```
10     (meta-analy$ or meta analy$ or metaanaly$).tw. (23115)
11     meta analysis.pt. (19624)
12     review academic.pt. (0)
13     review literature.pt. (0)
14     letter.pt. (634977)
15     review of reported cases.pt. (0)
16     historical article.pt. (250218)
17     review multicase.pt. (0)
18     8 or 9 or 10 or 11 or 12 or 13 (1424563)
19     14 or 15 or 16 or 17 (879842)
20     18 not 19 (1412320)
21     animal/ (4288697)
22     human/ (10444338)
23     21 and 22 (1066842)
24     21 not 23 (3221855)
25     20 not 24 (1302945)
26     7 and 25 (4)

Database: EMBASE <1980 to 2009 Week 05>
1      trauma.mp. or exp *"Wounds and Injuries"/ (405735)
2      exp *Mental Disorders/ (496419)
3      1 not 2 (387006)
4      Tranexamic Acid/ (3385)
5      3 and 4 (212)
6      limit 5 to (human and (english or german) and yr="1980 - 2009") (151)
7      from 6 keep (14)

Inclusion criteria for abstract selection
1      Systematic reviews
2      Meta-analyses

Exclusion criteria for abstract selection
1      Non-systematic reviews
```

Systematic medline, embase, and Cochrane library searches returned 16 citations. Apart from one, summarised in evidence table 9, none were developed systematically and therefore excluded. (Fig. 9)

Evidence Table 9: Tranexamic acid (secondary research)

Bibliographic Citation	Study Type	Evi-dence Level	Number of Patients	Primary studies included	Intervention	Comparison	Outcome Measure	Effect Size
Coats et al (2004) [115]	CSR	-	97	2 RCTs	Aprotinin	Aprotinin vs placebo	Proportion undergoing surgical intervention	Not evaluable
							Volume of blood transfused	Not evaluable
							Mortality	Not evaluable
	This Cochrane Review only included two trials, from 1979 and 1982, comprising a total of only 97 patients. Both studies were of questionable methodology. Allocation and concealment were unclear, and the results of one were reported in four papers. The review concluded that there was "insufficient evidence from randomised controlled trials of antifibrinolytic agents in trauma to either support or refute a clinically important treatment effect." Both the title and conclusions of this Cochrane review are misleading as both included trials investigated the effect of aprotinin, rather than other, or combinations of, antibrinolytics.							

Existing guidelines

```
Database: Ovid MEDLINE(R) <1950 to January Week 3 2009>
1      trauma.mp. or exp *"Wounds and Injuries"/ (486169)
2      exp *Mental Disorders/ (580167)
3      1 not 2 (472776)
4      Tranexamic Acid/ (1277)
5      3 and 4 (52)
6      limit 5 to yr="1980 - 2009" (42)
```

```
7      limit 6 to (english or german) (36)
8      guideline.pt. (14928)
9      7 and 8 (0)

Database: EMBASE <1980 to 2009 Week 05>
1      trauma.mp. or exp *"Wounds and Injuries"/ (405735)
2      exp *Mental Disorders/ (496419)
3      1 not 2 (387006)
4      Tranexamic Acid/ (3385)
5      3 and 4 (212)
6      limit 5 to (human and (english or german) and yr="1980 - 2009") (151)
7      Practice Guideline/ (101734)
8      6 and 7 (5)

Inclusion criteria for abstract selection
1      Guidelines

Exclusion criteria for abstract selection
1      Quasi-editorial guidelines
```

Systematic medline and embase searches for existing guidelines returned five citations. Three did not meet the inclusion criteria and were excluded. (Fig. 9) One other guideline was identified through manual cross-referencing, yielding a total of three relevant existing guidelines, summarised in evidence table 10.[19][55][116]

Evidence Table 10: Tranexamic acid (existing guidelines)

		Methodological assessment						
Biblio-graphic Citation	Summary	Scope and Purpose	Stake-holder Involve-ment	Rigour of Develop-ment	Clarity and Presen-tation	Applica-bility	Editorial Indepen-dence	Overall Assess-ment
Spahn et al (2007) [19]	This guideline extrapolates the evidence from studies of antifibrinolytic agents in elective surgery to trauma patients, and concludes that "antifibrinolytic agents (tranexamic acid, aminocaproic acid, or aprotinin) be considered in the treatment of the bleeding trauma patient. Antifibrinolytic therapy should be stopped once bleeding has been adequately controlled." It accords this recommendation a GRADE 2C.	89	50	71	75	11	100	+
Stainsby et al (2006) [55]	This guideline, based on previous reviews, concludes that there is insufficient evidence from randomised controlled trials of antibrinolytic agents in trauma to either support or refute a clinically important treatment effect. It does not make recommendations regarding their use.	78	25	38	50	44	100	+
Gaarder et al (2008) [116]	This guideline, based on previous reviews, concludes that there is no evidence for the routine use of antifibrinolytics in trauma. It recommends, however, that such therapy should be considered in cases of prolonged bleeding (>24h) and bleeding caused by hyperfibrinolysis, as identified by thromboelastography. It acknowledges that the diagnosis of hyperfibrinolysis in the absence of TEG is difficult. The methodology used to appraise the evidence base for this guideline is unclear.	89	50	33	50	44	100	+

Diagrammatic summary of evidence selection process

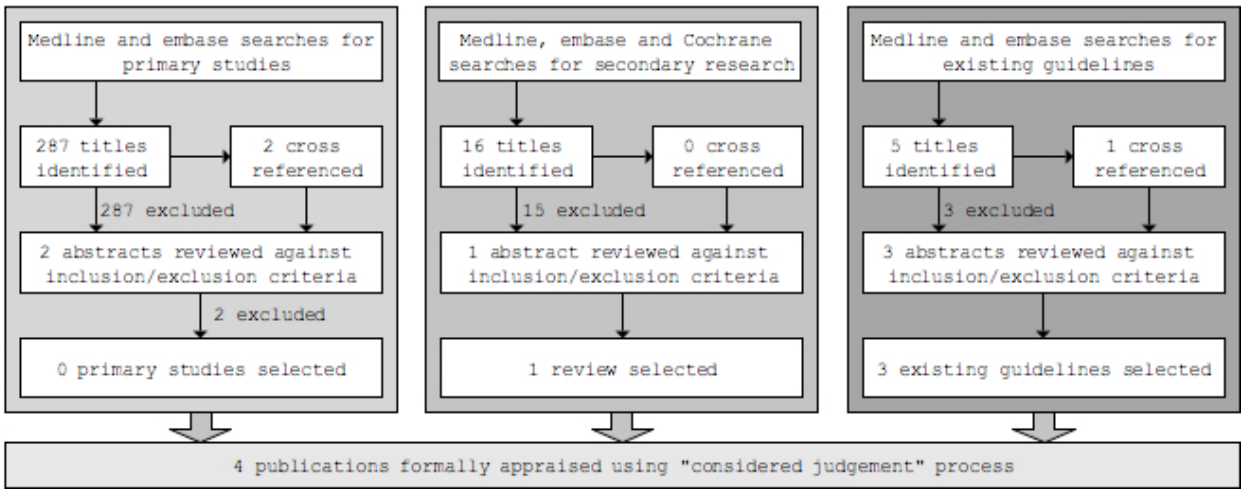

Fig 9. Diagrammatic summary of selection of literature relating to tranexamic acid

Appraisal

Volume of evidence: The volume of evidence for the use of any antifibrinolytics in trauma patients is poor. Other than two very small, outdated, methodologically questionable trials which are largely of historical interest, there are no primary studies to support such therapy. The paucity of primary studies is reflected, accurately, in the secondary literature. *Applicability:* There is, however, a very substantial body of high quality evidence, including several meta-analyses, to support the use of various antifibrinolytics in elective surgery, particularly cardiac, and liver transplantation. It is reasonable to extrapolate the benefits of antifibrinolytic agents to the trauma setting, but this assumption is not backed by any published data to suggest that the haemostatic response to trauma is similar to elective surgery.[19] The risk of precipitating thrombosis is a concern, but Henry et al's Cochrane review of antifibrinolytic use in the elective setting, which includes more than 8000 patients, demonstrated no increased risk of either arterial or venous thrombotic events.[110] *Consistency:* Given the lack of evidence, consistency in the trauma setting cannot be assessed. The effect of antifibrinolytics in the elective setting are, however, consistent.

Evidence statement

There is insufficient evidence from randomised trials of antifibrinolytic agents in trauma patients to either support or refute a clinically important treatment effect. However, given the proven efficacy and effectiveness of antifibrinolytics in reducing blood loss in elective surgery, and the lack of serious side effects, many authorities recommend the use of tranexamic acid in haemorrhaging trauma patients. This practice, although reasonable, amounts to "expert opinion" only, and no formal evidence statement has therefore been made.

Future research

The efficacy of tranexamic acid in the trauma setting is the subject of the ongoing, multinational CRASH (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) 2 study, in which 20,000 trauma patients are being randomly assigned to 1g of tranexamic acid for a period of 10 minutes followed by 1g infused for a period of 8 hours.[113][117] This trial should help to answer many of the questions surrounding tranexamic acid use in trauma, and allow stronger recommendations to be made.

3.3 PERMISSIVE HYPOTENSION

Haemorrhagic shock is failure of oxygen delivery, as a consequence of acute blood loss. Cellular ischaemia leads to organ dysfunction, and ultimately irreversible organ failure. The prevention and reversal of these sequelae through the rapid restoration of normal circulatory function – by replacing lost volume with a combination of synthetic fluids and blood products – was long regarded as pivotal, and remains enshrined in Advanced Trauma Life Support (ATLS) practice.[5][118][119] The recognition that fluid resuscitation may interfere with normal haemostatic mechanisms, ultimately exacerbating blood loss, however, led to a re-examination of this approach. [118][119] Permissive hypotension (also known as hypotensive resuscitation or balanced resuscitation) is a strategy of deferring or restricting fluid administration until control of haemorrhage has been achieved, while accepting a limited period of suboptimal end-organ perfusion. [119][120]

Key question

This section aims to answer the question "Does a strategy of withholding or limiting fluid resuscitation prior to surgical control of haemorrhage improve survival?"

Outcome measure

Mortality/survival.

Primary studies

```
Database: Ovid MEDLINE(R) <1950 to January Week 4 2009>
1      hypotensive resuscitation.mp. (46)
2      permissive hypotension.mp. or Hypotension, Controlled/ (1898)
3      balanced resuscitation.mp. (1)
4      trauma.mp. or exp *"Wounds and Injuries"/ (486815)
5      exp *Mental Disorders/ (580862)
6      4 not 5 (473395)
7      1 or 2 or 3 (1939)
8      6 and 7 (68)

Database: EMBASE <1980 to 2009 Week 05>
1      trauma.mp. or exp *"Wounds and Injuries"/ (405735)
```

```
2       exp *Mental Disorders/ (496419)
3       1 not 2 (387006)
4       permissive hypotension.mp. (18)
5       hypotensive resuscitation.mp. (44)
6       balanced resuscitation.mp. (0)
7       4 or 5 (57)
8       limit 7 to (human and (english or german) and yr="1980 - 2009") (29)

Inclusion criteria for abstract selection
1       Interventional studies
2       Observational studies

Exclusion criteria for abstract selection
1       Case reports
2       Case series without comparison groups
```

Systematic medline and embase searches returned 96 citations. 94 did not meet the inclusion criteria, and were therefore excluded. Manual cross-referencing revealed one further study. (Fig. 10) All three included studies are randomised controlled trials, summarised in table 11.

Evidence table 11: Permissive hypotension (primary studies)

Bibliographic Citation	Study Type	Evi-dence Level	Number of Patients	Patient Charac-teristics	Intervention	Comparison	Length of Follow-Up	Outcome Measure	Effect Size
Bickel et al (1994) [121]	CT	+	598	Penetrating torso trauma Hypotension (SAP <90 mmHg)	Withholding of fluid resuscitation	Early (pre-hospital or emergency room) (n=309) vs delayed (intra-operative) fluid resuscitation (n=289)	Until discharge	Mortality	Early 38% Delayed 30% RR for death with early fluid 1.25 (95% CI 1.00-1.58)*
	First large-scale study of hypotensive resuscitation concept. Suggestive of iv fluids being harmful in trauma patients with penetrating injury; some evidence of harm, no evidence of benefit. Although the study enrolled large numbers of patients, there was no concealment of allocation, and the trial therefore not truly randomised. Patients were also mostly young (median 36 years), and from a small geographical area, resulting in very short pre-hospital times. Extrapolation of the findings to other settings or mechanisms of injury may therefore not be appropriate. Despite these caveats, this study remains one of the most seminal studies of trauma management.								
Turner et al (2000) [122]	RCT	-	1309	Unselected (mostly blunt) adult trauma patients	Withholding of fluid resuscitation (unless transfer to hospital > 1h)	Conventional fluid resuscitation (as per ambulance service protocol) (n=699) vs delayed (no pre-hospital) fluid resuscitation (n=610)	Not stated	Mortality	Early (10.4%) Delayed/no (9.8%) RR for death with early fluid 1.06 (95%CI 0.77-1.47)*
	UK-based, cluster-randomised trial marred by vague inclusion criteria, resulting in the enrolment of a large number of patients with minor injuries. Numerous protocol violations, rendering the conclusions essentially meaningless: Only 31% in the conventional treatment group actually received intravenous fluids, and only 80% in the delayed treatment group actually had fluids withheld. If fluids given pre-theatre are included, the percentages are 49% vs 42%.								

Bibliographic Citation	Study Type	Evi-dence Level	Number of Patients	Patient Charac-teristics	Intervention	Comparison	Length of Follow-Up	Outcome Measure	Effect Size
Dutton et al (2002) [123]	RCT	-	110	Hypotensive (SAP < 90 mmHg) Blunt and penetrating	Withholding of fluid resuscitation	Controlled resuscitation (to titrate SAP to 70-80mmHg) (n=55) vs conventional resuscitation (SAP > 100mmHg) (n=55)		Mortality	Larger (7.3%) Smaller (7.3%) RR for death 1.00 (95% CI 0.26-3.81)*
	US-based trial marred by small numbers, lack of a power/sample size calculation, unclear methodology (no details on randomisation, concealment or compliance), and failure to achieve the proposed methodology: Patients in the "controlled resuscitation" group actually recorded a mean systolic blood pressure of 100mmHg. Conclusion: Insufficient evidence to suggest benefit or harm of resuscitation to different blood pressures.								

Relative risks (RR) from [124]

Secondary research

```
Database: Ovid MEDLINE® <1950 to January Week 4 2009>
1       hypotensive resuscitation.mp. (46)
2       permissive hypotension.mp. or Hypotension, Controlled/ (1898)
3       balanced resuscitation.mp. (1)
4       trauma.mp. or exp *"Wounds and Injuries"/ (486815)
5       exp *Mental Disorders/ (580862)
6       4 not 5 (473395)
7       1 or 2 or 3 (1939)
8       6 and 7 (68)
9       limit 8 to (humans and yr="1980 - 2009" and (english or german)) (37)
10      from 9 keep 3-4,15,20,23,25,27 (7)
11      meta-analysis/ (19687)
12      exp review literature/ (1408321)
13      (meta-analy$ or meta analy$ or metaanaly$).tw. (23200)
14      meta analysis.pt. (19687)
15      review academic.pt. (0)
16      review literature.pt. (0)
17      letter.pt. (635751)
18      review of reported cases.pt. (0)
19      historical article.pt. (250391)
20      review multicase.pt. (0)
21      11 or 12 or 13 or 14 or 15 or 16 (1426384)
22      17 or 18 or 19 or 20 (880782)
23      21 not 22 (1414118)
24      animal/ (4293014)
25      human/ (10456700)
26      24 and 25 (1068312)
27      24 not 26 (3224702)
28      23 not 27 (1304646)
29      28 and 9 (21)

Database: EMBASE <1980 to 2009 Week 05>
1       trauma.mp. or exp *"Wounds and Injuries"/ (405735)
2       exp *Mental Disorders/ (496419)
3       1 not 2 (387006)
4       permissive hypotension.mp. (18)
5       hypotensive resuscitation.mp. (44)
6       balanced resuscitation.mp. (0)
7       4 or 5 (57)
8       limit 7 to (human and (english or german) and yr="1980 - 2009") (29)

Inclusion criteria for abstract selection
1       Systematic reviews
2       Meta-analyses
```

```
Exclusion criteria for abstract selection
1       Non-systematic reviews
```

Systematic medline and embase searches returned 50 citations. Following review of the titles and abstracts, 49 were excluded as either irrelevant, or not meeting the inclusion criteria. The vast majority of excluded studies were non-systematic reviews or editorials. A search of the Cochrane library returned one further citation. (Fig. 10) Both reviews are summarised in evidence table 12.

Evidence Table 12: Permissive hypotension (secondary research)

Bibliographic Citation	Study Type	Evidence Level	Number of Patients	Primary studies included	Intervention	Comparison	Outcome Measure	Effect Size
Dretzke et al (2006) [125][126]	SR	+	2053	4 primary RCTs, including the three studies listed above	Withholding or limitation of fluid resuscitation	Withholding, limited or targeted resuscitation vs conventional resuscitation	Mortality	Not calculable
	High quality systematic review commissioned by the NHS Research & Development Health Technology Assessment programme, incorporating the three primary studies identified above, and one additional, small, early trial. This parallel randomised controlled trial of 36 patients compared a rapid infusor system with conventional practice. [127] The study was of poor methodological quality. Overall conclusion: There is no evidence to suggest that pre-hospital iv fluid resuscitation prior to control of bleeding is beneficial. There is limited evidence (from one study only) to suggest that it can be harmful, and that patients with penetrating injuries in particular may have better outcomes when fluids are withheld.							
Kwan et al (2003) [124]	CSR	+	1957	3 primary RCTs of patients with acute blood loss, including 1 not relating to trauma	Fluid administration	Early vs delayed fluid administration	Mortality	No meta-analysis performed (due to heterogeneity of primary studies)
	Cochrane systematic review, conducted in two parts. This first part of the review compared early with delayed fluid administration, and included 3 primary RCTs. Of these, only 2 relate to trauma (both included in the primary studies analysed above). [121][122]The remaining study was of patients with gastrointestinal haemorrhage. Conclusion: There is no evidence for or against the withholding of intravenous fluid administration in uncontrolled haemorrhage.							
	CSR	-	171	3 primary RCTs of patients with acute blood loss, including 1 not relating to trauma	Fluid administration	Larger vs smaller volume fluid administration	Mortality	No meta-analysis performed (due to heterogeneity of primary studies)
	Cochrane systematic review, conducted in two parts. This second part of the review compared larger with smaller volume fluid administration, and included 3 primary RCTs. All 3 trials were of trauma patients. One is included in the primary studies analysed above.[123] The remaining two are small, early studies, of questionable methodological quality. [127] Conclusion: There is no evidence for or against the administration of larger or smaller volumes of intravenous fluid in uncontrolled haemorrhage.							

Existing guidelines

```
Database: Ovid MEDLINE(R) <1950 to January Week 4 2009>
1       hypotensive resuscitation.mp. (46)
2       permissive hypotension.mp. or Hypotension, Controlled/ (1898)
3       balanced resuscitation.mp. (1)
4       trauma.mp. or exp *"Wounds and Injuries"/ (486815)
5       exp *Mental Disorders/ (580862)
6       4 not 5 (473395)
7       1 or 2 or 3 (1939)
8       6 and 7 (68)
9       guideline.pt. (14387)
10      8 and 9 (0)

Database: EMBASE <1980 to 2009 Week 05>
1       trauma.mp. or exp *"Wounds and Injuries"/ (405735)
2       exp *Mental Disorders/ (496419)
3       1 not 2 (387006)
```

```
4       permissive hypotension.mp. (18)
5       hypotensive resuscitation.mp. (44)
6       balanced resuscitation.mp. (0)
7       4 or 5 (57)
8       limit 7 to (human and (english or german) and yr="1980 - 2009") (29)
9       Practice Guideline/ (101983)
10      8 and 9 (2)

Inclusion criteria for abstract selection
1       Guidelines

Exclusion criteria for abstract selection
1       Quasi-editorial guidelines
```

Systematic medline and embase searches returned two citations, both of which were irrelevant and therefore exluded. (Fig. 10) Manual cross-referencing revealed a further two publications which met the inclusion criterion, and one paper which reports on the changes to the forthcoming eighth edition of the Advanced Trauma Life Support programme, although the revised manual is not yet available (evidence table 13).[19][120][128]

Evidence Table 13: Hypotensive resuscitation (existing guidelines)

		Methodological assessment						
Biblio-graphic Citation	Summary	Scope and Purpose	Stake-holder Involve-ment	Rigour of Develop-ment	Clarity and Presen-tation	Applica-bility	Editorial Indepen-dence	Overall Assess-ment
Kortbeek et al (2008) [120]	This article summarises the changes to the forthcoming (8th) Advanced Trauma Life Support (ATLS) guidelines. The new ATLS guidelines will place greater emphasis on the need to balance the risks of precipitating further bleeding against the adequacy of organ perfusion, by accepting a lower than normal blood pressure.	N/A*	N/A*	N/A*	N/A*	N/A*	N/A*	+
National Institute of Clinical Excellence (2008) [128]	This guideline recommends that, during pre-hospital management, "intravenous fluids should not be administered if a radial pulse can be felt (or, for penetrating torso injuries, if a central pulse can be felt)." It further recommends that "in the absence of a radial pulse (or a central pulse for penetrating torso injuries) in adults and older children […] intravenous fluid should be administered in boluses of no more than 250 ml. The patient should then be reassessed, and the process repeated until a radial pulse (or central pulse for penetrating torso injuries) is palpable."	100	100	100	100	50	100	+
Spahn et al (2007) [19]	This guideline recommends "a target systolic blood pressure of 80 to 100 mmHg, until major bleeding has been stopped […] in [patients] without brain injury" and accords this recommendation a GRADE 2C.	89	50	71	75	11	100	+

N/A* = Not applicable. This publication related to a forthcoming guideline. Methodology therefore cannot be assessed.

Diagrammatic summary of evidence selection process

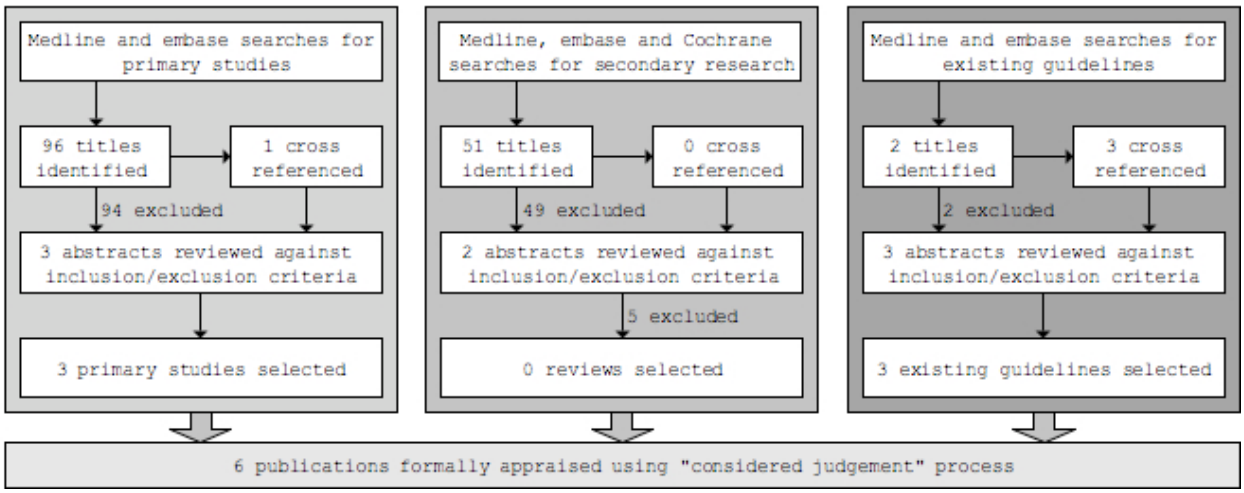

Fig 10. Diagrammatic summary of selection of literature relating to permissive hypotension.

Appraisal

Volume of evidence: The volume of evidence is moderate. There are three well-known major primary studies, all of which have significant methodological flaws.[121][122][123] Interestingly, the first of these trials, which showed a statistically significant difference between groups, was arguably the least flawed. [121] There are two systematic reviews, including one Cochrane systematic review.[124][125][126] The latter is marred by heterogeneity, as it included several trials pertaining to non-trauma patients (such as patients with gastrointestinal haemorrhage). *Applicability:* The Bickel trial only included patients with penetrating torso injuries, in the setting of a well-developed trauma system with very short pre-hospital times. [121] The findings are therefore not directly applicable to a typical European mixed (blunt/penetrating) trauma population, but may still be relevant to the management of subgroups of patients. The other two primary studies, by Turner and Dutton, are more applicable in terms of settings and inclusion criteria. [122][123] *Consistency:* The results of the primary studies are inconsistent. Only the Bickel trial showed a difference in mortality, but may not be applicable to all patients and settings (see above). [121] The Turner and Dutton trials, bearing in mind methological issues, were negative. [122][123]

Evidence statements

There is no new evidence to suggest that pre-hospital intravenous fluid resuscitation prior to control of bleeding is beneficial. There is, however, limited evidence to suggest that fluid resuscitation may be harmful, and that patients with penetrating injuries in particular may have better outcomes when fluids are withheld until surgical control of haemorrhage has been obtained.	1-

Future research

There is a need for a better quality trial of permissive hypotension in a clearly defined population, and to define the time period during which suboptimal end-organ perfusion is tolerated and reversible.

3.4 ACIDAEMIA MANAGEMENT

Acidaemia impairs all essential components of the coagulation process: At a pH of less than 7.4, platelets lose their pseudopodia and change shape, becoming more spherical.[65] Coagulation factor function is also impaired, through the induction of conformational changes, although different factors are affected by acidaemia in different ways. [65][129][130] Calcium binding sites have a pH-dependent affinity, further compounding the problem. [65] Restoration of normal acid-base status is therefore important.

The metabolic acidosis associated with haemorrhagic shock is the result of hypoperfusion. Correction requires the restoration of organ perfusion, but recognition of the need to defer volume replacement until control of haemorrhage has been obtained has led to a search for adjunctive pharmacological treatments to offset the pathophysiological consequences of acidaemia on other organ systems, and the coagulation system in particular. [129] The traditional treatment for severe lactic acidosis in critical illness is sodium bicarbonate, but there is little rationale for its use and no evidence of effectiveness.[131] Bicarbonate administration produces carbon dioxide, which requires large increases in minute volume to clear. Bicarbonate also decreases ionised calcium levels by approximately 10%, with consequent effects on coagulation and cardiac and vascular contractility.[131]

Ttris-hydroxymethyl aminomethane (THAM) is a biologically inert amino alcohol of low toxicity, which buffers carbon dioxide and acids *in vitro* and *in vivo*.[132] Its pK at 37°C is 7.8, making it a more effective buffer than bicarbonate.[132] In vivo, THAM supplements the buffering capacity of the blood bicarbonate system, accepting a proton, generating bicarbonate,

and decreasing the partial pressure of carbon dioxide in arterial blood.[132] It rapidly restores pH in acidaemia caused by carbon dioxide retention or metabolic acid accumulation. Unlike bicarbonate, which requires an open system for carbon dioxide elimination in order to exert its buffering effect, protonated THAM is excreted renally, avoiding issues with minute volume ventilation.[132] THAM has been used in the treatment of hypercapnoeic respiratory failure, diabetic and renal acidosis, salicylate and barbiturate intoxication, and raised intracranial pressure following cerebral trauma. It is also used in cardioplegic solutions and liver transplantation.[132] The administration of THAM in trauma patients with hypoperfusion-induced acidaemia is thus conceptually attractive, and has been the subject of several recent key publications.[3]

Key question

This section aims to answer the question "Does the administration of tris-hydroxymethyl aminomethane improve survival in trauma patients?"

Outcome measure

Mortality/survival

Primary studies

```
Database: Ovid MEDLINE(R) <1950 to January Week 4 2009>
1      trauma.mp. or exp *"Wounds and Injuries"/ (486815)
2      exp *Mental Disorders/ (580862)
3      1 not 2 (473395)
4      tris-hydroxymethyl aminomethane.mp. (3435)
5      Trometamol.mp. (210)
6      THAM.mp. (399)
7      4 or 5 or 6 (3723)
8      3 and 7 (71)
9      limit 8 to (humans and yr="1980 - 2009" and (english or german)) (29)
10     from 9 keep (0)

Database: EMBASE <1980 to 2009 Week 06>
1      tris-hydroxymethyl aminomethane.mp. or Trometamol/ (1934)
2      THAM.mp. (187)
3      1 or 2 (2030)
4      trauma.mp. or exp *"Wounds and Injuries"/ (406258)
5      exp *Mental Disorders/ (497136)
6      4 not 5 (387500)
7      3 and 6 (69)
8      limit 7 to human (39)
9      from 9 keep (0)

Inclusion criteria for abstract selection
1      Interventional studies
2      Observational studies

Exclusion criteria for abstract selection
1      Case reports
2      Case series without comparison groups
```

Systematic medline and embase searches returned no primary studies of THAM in the setting of non-cerebral trauma, although there are numerous publications relating to the use of THAM for neuroprotection following traumatic brain injury.

Secondary research

```
Database: Ovid MEDLINE(R) <1950 to January Week 4 2009>
1      trauma.mp. or exp *"Wounds and Injuries"/ (486815)
2      exp *Mental Disorders/ (580862)
3      1 not 2 (473395)
4      tris-hydroxymethyl aminomethane.mp. (3435)
5      Trometamol.mp. (210)
6      THAM.mp. (399)
7      4 or 5 or 6 (3723)
8      3 and 7 (71)
9      limit 8 to (humans and yr="1980 - 2009" and (english or german)) (29)
10     from 9 keep (0)

Database: EMBASE <1980 to 2009 Week 06>
1      tris-hydroxymethyl aminomethane.mp. or Trometamol/ (1934)
2      THAM.mp. (187)
3      1 or 2 (2030)
4      trauma.mp. or exp *"Wounds and Injuries"/ (406258)
5      exp *Mental Disorders/ (497136)
6      4 not 5 (387500)
7      3 and 6 (69)
8      limit 7 to human (39)
9      from 8 keep (1)

Inclusion criteria for abstract selection
1      Systematic reviews
2      Meta-analyses

Exclusion criteria for abstract selection
1      Non-systematic reviews
```

Systematic medline, embase and Cochrane library searches returned only one review article (and guideline) of the treatment of acidaemia with THAM, which was developed non-systematically, and makes no recommendations regarding the use of THAM in non-cerebral trauma.[132]

Existing guidelines

```
Database: Ovid MEDLINE(R) <1950 to January Week 4 2009>
1      trauma.mp. or exp *"Wounds and Injuries"/ (486815)
2      exp *Mental Disorders/ (580862)
3      1 not 2 (473395)
4      tris-hydroxymethyl aminomethane.mp. (3435)
5      Trometamol.mp. (210)
6      THAM.mp. (399)
7      4 or 5 or 6 (3723)
8      3 and 7 (71)
9      limit 8 to (humans and yr="1980 - 2009" and (english or german)) (29)
10     from 9 keep 0 (0)

Database: EMBASE <1980 to 2009 Week 06>
1      tris-hydroxymethyl aminomethane.mp. or Trometamol/ (1934)
2      THAM.mp. (187)
3      1 or 2 (2030)
4      trauma.mp. or exp *"Wounds and Injuries"/ (406258)
5      exp *Mental Disorders/ (497136)
6      4 not 5 (387500)
7      3 and 6 (69)
8      limit 7 to human (39)
```

```
9      from 8 keep 1-39 (39)
10     Practice Guideline/ (101983)
11     9 and 10 (1)
12     from 11 keep 1 (1)

Inclusion criteria for abstract selection
1      Guidelines

Exclusion criteria for abstract selection
1      Quasi-editorial guidelines
```

Systematic medline, embase and Cochrane library searches returned only one guideline of the treatment of acidaemia with THAM, which was developed non-systematically, and makes no recommendations regarding the use of THAM in non-cerebral trauma.[132]

Evidence statement

There is no evidence to support the use of tris-hydroxymethyl aminomethane in trauma patients.

Future research

There is a need for a trial of THAM in acidaemic trauma patients.

3.5 HYPOTHERMIA MANAGEMENT

Environmental exposure combined with limited endogenous heat production, as a consequence of hypoperfusion-induced anaerobic metabolism, leads to hypothermia, which may be compounded by injudicious administration of cold resuscitation fluids and blood. The detrimental effects of hypothermia on protease and platelet function and metabolism are well recognised.[46][65] However, hypothermia probably has disproportionately greater effects on platelet function than on serine proteases.[3][46][65]

Two large, well-conducted retrospective studies, which controlled for injury severity, have shown hypothermia to be an independent predictor of mortality after major trauma. Wang et al, in a study of 38520 trauma patients, of which 1921 (5%) had a core temperature of <35°C on admission, showed that hypothermia was independently associated with increased odds of death (OR 3.03, 95%CI 2.62-3.51).[133] Martin et al studied the outcome of 11828 trauma patients with an admission temperature of <35°C, and found the odds of death to be 1.54 (95%CI 1.40-1.71).[134] Recognition of the association between hypothermia, coagulopathy, and adverse outcome has led to the widespread acceptance of aggressive hypothermia mitigation in trauma patients. Although hypothermia mitigation is also important in non-trauma surgery, the special demands of trauma management, and in particular the need to prepare large areas of the body for immediate extension of surgical access, limit the use of conventional warming devices, and poses special problems.

Key question

This section aims to answer the questions “Do aggressive attempts at hypothermia mitigation improve outcome in trauma patients?” and “What is the most effective method of preventing and treating hypothermia in trauma patients?”

Outcome measure

Mortality/survival; change in temperature

Primary studies

```
Database: Ovid MEDLINE(R) <1950 to January Week 4 2009>
1      trauma.mp. or exp *"Wounds and Injuries"/ (487169)
2      exp *Mental Disorders/ (580839)
3      1 not 2 (473749)
4      *Hypothermia/ (4795)
5      3 and 4 (438)
6      limit 5 to (humans and yr="1980 - 2009" and (english or german)) (295)
7      randomized controlled trial.pt. (262320)
8      controlled clinical trial.pt. (78055)
9      randomized controlled trials/ (57544)
10     random allocation/ (62690)
11     double-blind method/ (98628)
12     single-blind method/ (12432)
13     7 or 8 or 9 or 10 or 11 or 12 (443309)
14     animal/ (4302436)
15     human/ (10485618)
16     14 and 15 (1071730)
17     14 not 16 (3230706)
18     13 not 17 (413856)
19     6 and 18 (8)

Database: EMBASE <1980 to 2009 Week 06>
1      trauma.mp. or exp *"Wounds and Injuries"/ (406258)
2      exp *Mental Disorders/ (497136)
3      1 not 2 (387500)
4      *Hypothermia/et, dm, co, di, th, pc, su [Etiology, Disease Management,
       Complication, Diagnosis, Therapy, Prevention, Surgery] (910)
5      3 and 4 (893)
6      limit 5 to (human and (english or german)) (621)
7      trauma.m_titl. (25350)
8      6 and 7 (21)
9      from 8 keep (6)

Inclusion criteria for abstract selection
1      Interventional studies

Exclusion criteria for abstract selection
1      Case reports
2      Case series without comparison groups
```

Systematic medline and embase searches returned 29 citations. Following review of the titles, 15 were excluded as irrelevant. (Fig. 11) Of the remaining 14 publications, 3 met the inclusion criteria (table 14).

Evidence table 14: Hypothermia mitigation (primary studies)									
Bibliographic Citation	Study Type	Evi-dence Level	Number of Patients	Patient Charac-teristics	Intervention	Comparison	Length of Follow-Up	Outcome Measure	Effect Size
Cohen et al (2002) [135]	RCT	+	298	Normo-thermic (>35°C) trauma patients admitted to emergency department ISS<15	Heat loss prevention	Reflective blanket over warmed cotton blanket vs forced-warm-air inflatable blanket vs 3 cotton warmed blankets	To discharge from emergency department	Temperature	Warmed blankets: pre 36.8°C vs post 37.3°C Reflective: pre 36.9°C vs post 37.6°C Forced-air: pre 36.8°C vs post 37.3°C (p>0.05)
	Trial of three different types of heat loss prevention strategies in normothermic, non-severely injured trauma patients. No difference observed. May not be applicable to patients who are hypothermic on admission.								
Kober et al (2001) [136]	RCT	+	100	Hypothermic (mean 35.4/ 35.3°C) "Minor trauma" During transfer to hospital	Electric warming blanket	Electric warming blanket switched on vs switched off	To arrival at hospital	Temperature	Blanket off: Change -0.4 °C (95%CI -0.3 to -0.5) Blanket on: Change 0.8 °C (95%CI 0.7-0.9)
	Small trial conducted by paramedic-manned ambulances, accounting for limitation to patients with "minor" (not otherwise specified) trauma. Electric blankets raised temperature more than passive warming.								
Gentilello et al (1997) [137]	RCT		57	Hypothermic (<=35.5°C) "Critically injured" ISS 32 (SR) vs 31 (CAVR) With PAFC in situ	Rewarming	Continuous arteriovenous (femoro-femoral) rewarming (CAVR) vs Standard rewarming (SR)	To discharge	Mortality	Not clearly stated (see below)
	Randomised trial which set out to evaluate whether hypothermia during resuscitation is protective or harmful by comparing hypothermic patients who had been treated with conventional rewarming methods, or rapid rewarming by arteriovenous extracorporeal warming. Statistical methods and presentation of findings is confusing, but appear to show an excess early mortality in patients treated with standard rewarming. However, late deaths reduced the overall survival to discharge advantage in patients who underwent CAVR, which was attributed to survival from injuries which patients who underwent SR did not survive. The author's concluded that hypothermia increases the risk of early death after injury.								

Secondary research

```
Database: Ovid MEDLINE(R) <1950 to January Week 4 2009>
1       trauma.mp. or exp *"Wounds and Injuries"/ (487169)
2       exp *Mental Disorders/ (580839)
3       1 not 2 (473749)
4       *Hypothermia/ (4795)
5       3 and 4 (438)
6       limit 5 to (humans and yr="1980 - 2009" and (english or german)) (295)
7       meta-analysis/ (19805)
8       exp review literature/ (1412791)
9       (meta-analy$ or meta analy$ or metaanaly$).tw. (23318)
10      meta analysis.pt. (19805)
11      review academic.pt. (0)
12      review literature.pt. (0)
13      letter.pt. (637017)
14      review of reported cases.pt. (0)
15      historical article.pt. (251109)
16      review multicase.pt. (0)
17      7 or 8 or 9 or 10 or 11 or 12 (1430930)
18      13 or 14 or 15 or 16 (882749)
```

```
19      17 not 18 (1418630)
20      animal/ (4302436)
21      human/ (10485618)
22      20 and 21 (1071730)
23      20 not 22 (3230706)
24      19 not 23 (1308903)
25      6 and 24 (69)
27      from 25 keep (15)

Database: EMBASE <1980 to 2009 Week 06>
1       trauma.mp. or exp *"Wounds and Injuries"/ (406258)
2       exp *Mental Disorders/ (497136)
3       1 not 2 (387500)
4       *Hypothermia/et, dm, co, di, th, pc, su [Etiology, Disease Management,
        Complication, Diagnosis, Therapy, Prevention, Surgery] (910)
5       3 and 4 (893)
6       limit 5 to (human and (english or german)) (621)
7       trauma.m_titl. (25350)
8       6 and 7 (21)
9       from 8 keep (5)

Inclusion criteria for abstract selection
1       Systematic reviews
2       Meta-analyses

Exclusion criteria for abstract selection
1       Non-systematic reviews
```

No methodologically rigorous secondary research was identified. Systematic medline and embase searches returned 90 citations. 70 of these were deemed irrelevant on the basis of title review and excluded. None of the remaining 20 publications met the inclusion criteria. A search of the Cochrane library similarly revealed no systematic reviews of interventions to mitigate against hypothermia in trauma patients. (Fig. 11)

Existing guidelines

```
Database: Ovid MEDLINE(R) <1950 to January Week 4 2009>
1       trauma.mp. or exp *"Wounds and Injuries"/ (487169)
2       exp *Mental Disorders/ (580839)
3       1 not 2 (473749)
4       *Hypothermia/ (4795)
5       3 and 4 (438)
6       limit 5 to (humans and yr="1980 - 2009" and (english or german)) (295)
7       guideline.pt. (14427)
8       6 and 7 (1)
9       from 8 keep 1 (1)

Database: EMBASE <1980 to 2009 Week 06>
1       trauma.mp. or exp *"Wounds and Injuries"/ (406258)
2       exp *Mental Disorders/ (497136)
3       1 not 2 (387500)
4       *Hypothermia/et, dm, co, di, th, pc, su [Etiology, Disease Management,
        Complication, Diagnosis, Therapy, Prevention, Surgery] (910)
5       3 and 4 (893)
6       limit 5 to (human and (english or german)) (621)
7       *Practice Guideline/ (8140)
8       6 and 7 (1)
9       from 8 keep 1 (1)

Inclusion criteria for abstract selection
1       Guidelines

Exclusion criteria for abstract selection
```

Systematic medline and embase searches returned no relevant citations. Manual cross-referencing revealed two guidelines, one of which has been mentioned previously.[19][138] (Fig. 11)

Evidence Table 15: Hypothermia mitigation (existing guidelines)

		Methodological assessment						
Biblio-graphic Citation	Summary	Scope and Purpose	Stake-holder Involve-ment	Rigour of Develop-ment	Clarity and Presen-tation	Applica-bility	Editorial Indepen-dence	Overall Assess-ment
Spahn et al (2007) [19]	This guideline recommends that "early application of measures to reduce heat loss and warm the hypothermic patient in order to achieve and maintain normothermia" should be employed, and accords this recommendation a GRADE 1C.	89	50	71	75	11	100	+
National Institute of Clinical Excellence [138]	This guideline, which is not limited to trauma patients, but is aimed at all surgical patients at risk of inadvertent hypothermia, recommends that forced air warming should be started preoperatively if the patient's temperature is <36°C, and should be maintained throughout the intraoperative phase.	100	100	100	100	33	100	+

Diagrammatic summary of evidence selection process

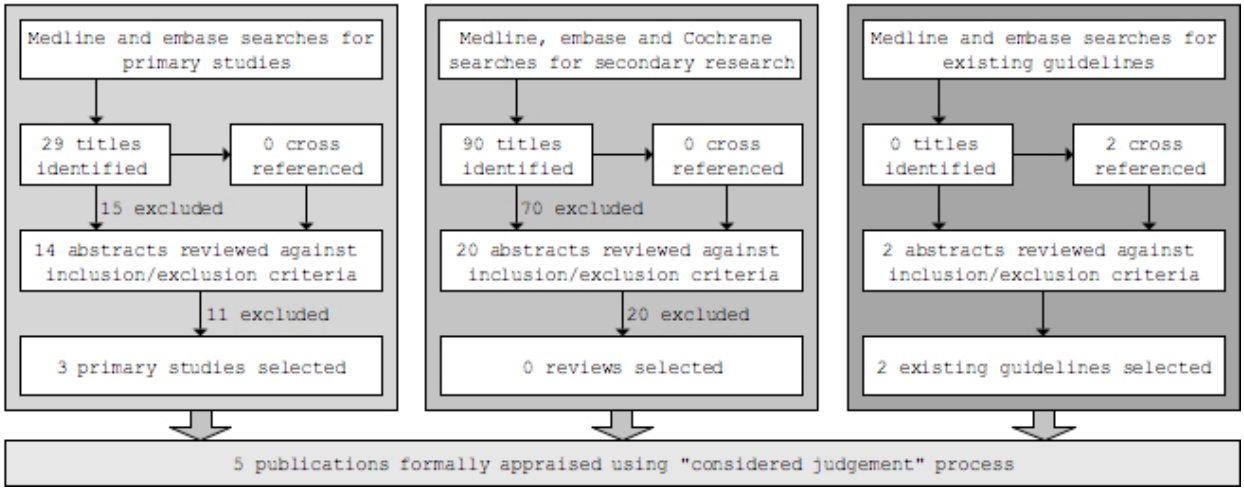

Fig 11. Diagrammatic summary of selection of literature relating to hypothermia mitigation

Appraisal

Volume of evidence: Although there is limited evidence from trials, there is a high volume of evidence from observational studies. *Applicability:* The publications cited above are broadly applicable to the target population of this guideline, although few of the comparisons of different devices were specifically conducted in the trauma setting. The mechanisms underlying the development of hypothermia may differ between trauma and non-trauma patients, and because surgical intervention in trauma patients often requires wide access. *Consistency:* The evidence showing the detrimental effects of hypothermia is consistent. The evidence supporting the use of any one device, or combination of devices, is inconsistent. Although there is no direct evidence

to support their use, electrical warming mattresses are the most practical devices. These devices are effective and do not compromise access.

Evidence statements

Hypothermia in trauma patients is associated with increased mortality. Reversal of hypothermia is associated with improved survival. Hypothermia in trauma patients should therefore be prevented whenever possible, and aggressively treated when present.	2+
There is no evidence to support the use of extracorporeal warming techniques, such as cardiopulmonary or passive arteriovenous bypass, as sometimes used for the treatment of severe hypothermia due to prolonged exposure or drowning, for the treatment of trauma-associated hypothermia. These systems are cumbersome to set up and use, are associated with risks such as thrombosis and haemorrhage due to decannulation, and may be contraindicated if anticoagulation is required. The use of cavity rewarming techniques such as peritoneal or pleural lavage is also impractical, and there is no evidence of its utility in trauma.	2-

3.6 DAMAGE CONTROL SURGERY

Damage control is a surgical strategy which sacrifices the completeness of the immediate repair in order to address the combined physiological impact of injury and operation.[12] It was born out of the realisation that the physiological derangements caused by haemorrhagic shock – the lethal triad of acidosis, coagulopathy, and hypothermia – were the prime determinants of outcome, and exacerbated by prolonged surgery.[12] The aim of treatment was shifted from restoring anatomical integrity to limiting the duration of the operation, thus facilitating aggressive post-operative resuscitation in the intensive care unit.[12] If the patient recovered, anatomical integrity was restored at "relook" laparotomy some hours or days later.

Pringle first enunciated the principles of compression and hepatic packing for control of portal venous haemorrhage in the early part of the twentieth century, but these techniques fell from favour during the second world war and Vietnam war, where definitive primary surgery became the preferred treatment.[139][140] The technique started to re-emerge in the late 1970s. In 1976, Lucas et al reported three patients with severe liver injuries, who survived with perihepatic packing.[141] In 1978, Calne et al described another four cases in whom exsanguinating liver

haemorrhage was temporarily controlled with gauze packing, enabling safe transfer and definitive management at a more appropriate institution.[142] All four patients survived. In 1981, Feliciano et al reported a 90% survival in 10 patients with exsanguinating intra-abdominal haemorrhage managed with packing, and in 1983, Stone et al were the first to describe temporising manoeuvres for hollow viscera and the urinary tract, and to divide the damage control sequence into phases.[143][144] The concept continued to evolve, and by the end of the decade, more than 1,000 cases had been described in the literature, many of them included in two major reviews published in 1997 and 2000.[10][140][141][142][143][144][145][146][147][148][149][150][151][152][153][154][155][156][157][158][159][160][161][162][163][164]

Damage control surgery was originally stratified into three distinct phases.[12][144] The first is abbreviated resuscitative surgery for rapid control of haemorrhage and contamination.[12][163] The essence of this phase is speed, and traditional definitive primary repairs are deferred in favour of rapid measures to control haemorrhage, restore blood flow where needed, and control or contain contamination.[12][163] Intra-abdominal packing and temporary abdominal closure complete this critical first phase.[12][163] The second phase constitutes aggressive resuscitation in the intensive care unit, consisting of rewarming, correction of coagulopathy, and optimisation of haemodynamic status and reversal of acidosis.[12][163] When normal physiology has been restored, re-exploration is undertaken for definitive management of injuries and abdominal closure (phase 3).[12][163] In 2001, Johnson and Schwab introduced a fourth component to the damage control sequence, “damage control ground 0”.[12][165] This represents the earliest phase of the damage control process, which occurs in the prehospital setting, and continues into the trauma bay.[166] The emphasis is on injury-pattern recognition for potential damage control beneficiaries.

The initial damage control laparotomy (phase 1) consists of three key manouevres: Obtaining control of haemorrhage, obtaining control of contamination, and temporary abdominal closure. Control of haemorrhage is obtained by initial digital compression, followed – as appropriate – by application of vascular clamps or placement of packs. Distinction should be made between initial, resuscitative; and subsequent, therapeutic packing.[163] Resuscitative “four-quadrant” packing, maintained for a few minutes, is used as an initial short-term measure to control or minimise further blood loss while attending to other, higher priority injuries, or allowing the anaesthetist time to “catch up”.[163] Therapeutic packing, in contrast, provides tamponade of bleeding when it is surgically unmanageable or coagulopathy has developed.[163] It is used to enable a longer period of resuscitation, or occasionally to access other means of definitive

vascular control, such as angioembolisation.[163] The principles of packing are to exert sufficient pressure to stop bleeding, while attempting to restore normal anatomy (eg. by reapproximating liver parenchyma, rather than separating it), and without precipitating compartment syndrome or impeding caval return. Packing is an adjunct, and should not be regarded as a substitute for obtaining control of vessels which can be ligated, repaired, or shunted.[163]

Contamination is controlled by suturing, stapling (using the linear cutter-stapler family of devices), or tying off hollow viscus injuries, with or without resection.[12]

Temporary abdominal closure reduces the risk of abdominal compartment syndrome, allows the monitoring of ongoing blood losses, and facilitates re-entering the abdomen for removal of packs and definitive repairs.[12] The "Bogota Bag", consisting of an opened-up bag of intravenous fluid sutured to the skin edges, is the traditional method of coverage, but has fallen out of favour because exudate and blood are not drained. Fluid runs from underneath the dressing and collects underneath the patient, making nursing care very difficult. Topical negative suction dressings, such as the improvised "OpSite Sandwich",[167] or commercially available alternatives, are much cleaner and easier to look after.

Although there are many other techniques which are occasionally necessary – for example balloon tamponade of a penetrating liver injury – the methods described above are those most frequently used in damage control surgery, and are therefore appraised and evaluated in detail in the following sections.

The evaluation of damage control surgery is complicated by the heterogeneity of the target group and the intervention. There is no clear definition of what constitutes a damage control operation, or when it is indicated. Available evidence can be divided into those studies which assess the global effectiveness of the strategy, irrespective of differences in injury type and burden, and surgical and non-surgical management, and those which evaluate specific aspects, such as perihepatic packing. For the purpose of this review, these studies have been analysed together. The evaluation of damage control surgery within the context of haemostatic resuscitation is further complicated by the fact that the vast majority of studies were performed prior to the introduction of damage control resuscitation principles.

Key question

This section aims to answer the question "Does the use of damage control surgical techniques improve survival in trauma patients with severe bleeding?"

Outcome measure

Mortality/survival.

Primary studies

```
Database: Ovid MEDLINE(R) <1950 to November Week 3 2008>
1      trauma.mp. or exp *"Wounds and Injuries"/ (505433)
2      exp *Mental Disorders/ (605325)
3      1 not 2 (491574)
4      damage control.mp. [mp=title, original title, abstract, name of substance word,
       subject heading word] (532)
5      ((staged or abbreviated) and laparotomy).mp. [mp=title, original title,
       abstract, name of substance word, subject heading word] (382)
6      laparostomy.mp. [mp=title, original title, abstract, name of substance word,
       subject heading word] (161)
7      4 or 5 or 6 (1030)
8      3 and 7 (440)
9      from 8 keep (97)
10     packing.mp. (13666)
11     exp Liver/ (332191)
12     3 and 11 (5139)
13     10 and 12 (147)
14     limit 13 to (english or german) (119)
15     from 13 keep (8)

Database: EMBASE <1980 to 2009 Week 05>
1      trauma.mp. or exp *"Wounds and Injuries"/ (405735)
2      exp *Mental Disorders/ (496419)
3      1 not 2 (387006)
4      damage control.mp. (462)
5      (((staged or abbreviated) and laparotomy) or laparostomy).mp. [mp=title,
       abstract, subject headings, heading word, drug trade name, original title,
       device manufacturer, drug manufacturer name] (434)
6      3 and 4 and 5 (26)
7      from 6 keep 1-26 (26)
8      packing.mp. [mp=title, abstract, subject headings, heading word, drug trade
       name, original title, device manufacturer, drug manufacturer name] (11953)
9      exp Liver/ (207896)
10     3 and 8 and 9 (33)
11     limit 10 to human (24)
12     from 11 keep 6,16 (2)

Inclusion criteria for abstract selection
1      Interventional studies
2      Observational studies

Exclusion criteria for abstract selection
1      Case reports
2      Case series without comparison groups
```

Systematic searches across medline and embase returned 609 citations. As some of the early studies on damage control surgery were published before 1980, no limitation was placed on publication date in the medline searches. Following review of the titles, 476 were excluded as irrelevant. On review of the remaining 133 abstracts, and the abstracts of a further 33 manually cross-referenced papers, only four were deemed to meet the inclusion criteria. (Fig. 12) The vast majority of the excluded studies, including many seminal and often-quoted papers on the subject, consist of case series without concurrent or even historical controls. [142][143][146][148]

[149][150][151][153][154][155][157][159][160][168] The remaining four papers are appraised in evidence table 16.

Evidence table 16: Damage control surgery (primary studies)

Bibliographic Citation	Study Type	Evi-dence Level	Number of Patients	Patient Charac-teristics	Intervention	Comparison	Length of Follow-Up	Outcome Measure	Effect Size
Stone HH et al (1983) [144]	NCCS	+	31	Coagulopathy (not otherwise specified)	Damage control surgery (gastrointestinal ligation, ureteric ligation, packing)	Conventional laparotomy (CL) (n=14) Damage control surgery (DCS) (n=17)	To discharge	Survival	CL 7% DCS 65%
	Seminal early paper comparing two groups of consecutive patients undergoing definitive primary repair and damage control surgery, encompassing packing, gastrointestinal resection without anastomosis, and repair of major vascular injuries. Numbers of patients in each group small. Possibility of confounders due to design and age of paper.								
Ivatury RR et al (1986) [147]	NCCS	+	345	Hepatic injury	Perihepatic packing	Conventional treatment (CT) (1977-1980) (n=177) Perihepatic packing (PP) (1981-1985) (n=168)	To discharge?	Mortality from haemorrhage	CT 19.2% PP 19.4%
	Larger study comparing periphepatic packing with historical, conventionally managed cohort. No difference in mortality from haemorrhage. Possibility of confounders due to design and age of paper.								
Rotondo MF et al (1993) [10]	NCCS	+	46	Penetrating abdominal trauma >10 U transfusion	Damage control (DCS)	Damage control (DCS) (n=24) vs definitive primary repair (DPR) (n=22)	To discharge	Survival	DCR 55% vs DPR 58%
	Small study of patients with major penetrating abdominal injuries managed with either damage control surgery (using a variety of techniques) or conventional definitive primary repair. Allocation unclear. No difference in survival. Possibility of confounders due to design and age of paper.								
		+	22	Penetrating abdominal trauma >10 U transfusion Major vascular injury >1 Visceral injury	Damage control (DCS)	Damage control (DCS) (n=13) vs definitive primary repair (DPR) (n=9)	To discharge	Survival	DCR 77% vs DPR 11% (p<0.02)
	Subgroup analysis of above study, of severely injured patients, defined as having sustained a major vascular injuries and two or more visceral injuries. Statistically significant difference in survival. Numbers of patients were small, and the study design predisposes to confounding.								
Johnson JW et al (2001) [165]	NCCS	+	45	Penetrating abdominal trauma, majority gunshot wounds	Damage control surgery	Damage control surgery 1997-2000 (DCS-C) (n=21) Damage control surgery historical (DCS-H) (n=24)	To discharge	Survival	DCS-C 90% DCS-H 58% (p=0.02)
	Only recent comparative study, and only study comparing contemporary and historical cohorts, both managed with damage control surgical techniques. Groups were small but broadly comparable in terms of injury severity score (ISS), penetrating abdominal trauma index (PATI), and physiological manifestations of injury (revised trauma score, RTS). The historical group were more hypothermic on commencement of laparotomy than the current group. The current group were less coagulopathic and hypothermic on admission to ICU, despite having received less blood products. This may have translated into improved survival, and represents an important confounder.								

Secondary research

```
Database: Ovid MEDLINE(R) <1950 to January Week 3 2009>
1      trauma.mp. or exp *"Wounds and Injuries"/ (486169)
2      exp *Mental Disorders/ (580167)
3      1 not 2 (472776)
4      damage control.mp. [mp=title, original title, abstract, name of substance word,
       subject heading word] (534)
5      ((staged or abbreviated) and laparotomy).mp. [mp=title, original title,
       abstract, name of substance word, subject heading word] (380)
6      laparostomy.mp. [mp=title, original title, abstract, name of substance word,
       subject heading word] (161)
7      packing.mp. [mp=title, original title, abstract, name of substance word,
       subject heading word] (13671)
8      4 or 5 or 6 or 7 (14632)
9      3 and 8 (983)
10     meta-analysis/ (19624)
11     exp review literature/ (1406546)
12     (meta-analy$ or meta analy$ or metaanaly$).tw. (23115)
13     meta analysis.pt. (19624)
14     review academic.pt. (0)
15     review literature.pt. (0)
16     letter.pt. (634977)
17     review of reported cases.pt. (0)
18     historical article.pt. (250218)
19     review multicase.pt. (0)
20     10 or 11 or 12 or 13 or 14 or 15 (1424563)
21     16 or 17 or 18 or 19 (879842)
22     20 not 21 (1412320)
23     animal/ (4288697)
24     human/ (10444338)
25     23 and 24 (1066842)
26     23 not 25 (3221855)
27     22 not 26 (1302945)
28     guideline.pt. (14382)
29     9 and 27 (181)
30     limit 29 to (humans and yr="1980 - 2009" and (english or german)) (144)
31     from 30 keep 4-6,10,15,18,22,34-35,39,42-43,46,58,72-
       73,81,84,87,89,94,98,100,108,117,126-128,132,134 (30)

Database: EMBASE <1980 to 2009 Week 07>
1      trauma.mp. or exp *"Wounds and Injuries"/ (406671)
2      exp *Mental Disorders/ (497727)
3      1 not 2 (387898)
4      damage control.mp. (467)
5      (((staged or abbreviated) and laparotomy) or laparostomy).mp. [mp=title,
       abstract, subject headings, heading word, drug trade name, original title,
       device manufacturer, drug manufacturer name] (436)
6      packing.mp. (11998)
7      4 and (5 or 6) (77)
8      "Review"/ (931130)
9      7 and 8 (23)

Inclusion criteria for abstract selection
1      Systematic reviews
2      Meta-analyses

Exclusion criteria for abstract selection
1      Non-systematic reviews
```

Systematic medline searches for meta-analyses and systematic reviews using the NHS Centre for Reviews and Dissemination's filter returned 144 citations, and embase searches a further 23. 134 of these were excluded as irrelevant on the basis of a review of titles, leaving 33 abstracts. (Fig.

12) The majority were found to be non-systematic reviews and excluded, leaving two articles for inclusion in the formal appraisal,[169][170] of which one could not be located.[170] These studies are appraised in evidence table 17. A search of the Cochrane Library revealed a protocol for a systematic review, but no completed works.[171] Manual cross-referencing did not identify any additional systematic reviews or meta-analyses. Two frequently quoted reviews were not included in this analysis.[163][164] Although these reviews contain large numbers of patients, almost all of the primary studies were simple case series, rather than comparative studies.

Evidence Table 17: Damage control surgery (secondary research)

Bibliographic Citation	Study Type	Evi-dence Level	Number of Patients	Primary studies included	Intervention	Comparison	Outcome Measure	Effect Size
Matthes et al (2006) [169]	SR	+	77	2 small comparative studies (with historical control groups)	Damage control surgery	Damage control vs primary definitive surgery	Mortality (not further defined)	61% RR (95%CI 41-81%)
	Systematic review of several strategies in abdominal trauma management. The use of damage control surgery constituted only a small part of the analysis. The two studies included are both mentioned above.[11][144] The calculation of effect size and confidence interval is unclear. This review also mentioned several of the case series mentioned above and summarised in Shapiro and Rotondo's reviews.[163][164]							

Existing guidelines

```
Database: Ovid MEDLINE(R) <1950 to January Week 3 2009>
1       trauma.mp. or exp *"Wounds and Injuries"/ (486169)
2       exp *Mental Disorders/ (580167)
3       1 not 2 (472776)
4       damage control.mp. [mp=title, original title, abstract, name of substance word,
        subject heading word] (534)
5       ((staged or abbreviated) and laparotomy).mp. [mp=title, original title,
        abstract, name of substance word, subject heading word] (380)
6       laparostomy.mp. [mp=title, original title, abstract, name of substance word,
        subject heading word] (161)
7       packing.mp. [mp=title, original title, abstract, name of substance word,
        subject heading word] (13671)
8       4 or 5 or 6 or 7 (14632)
9       3 and 8 (983)
10      guideline.pt. (14382)
11      9 and 10 (181)
12      limit 11 to (humans and yr="1980 - 2009" and (english or german)) (144)
13      from 12 keep 4-6,10,15,18,22,34-35,39,42-43,46,58,72-
        73,81,84,87,89,94,98,100,108,117,126-128,132,134 (30)

Database: EMBASE <1980 to 2009 Week 05>
1       trauma.mp. or exp *"Wounds and Injuries"/ (405735)
2       exp *Mental Disorders/ (496419)
3       1 not 2 (387006)
4       Practice Guideline/ (101734)
5       3 and 4 (3542)
6       damage control.mp. (462)
7       5 and 6 (12)
8       from 7 keep 4 (1)

Inclusion criteria for abstract selection
1       Systematically developed guidelines

Exclusion criteria for abstract selection
1       Quasi-editorial guidelines
```

Systematic searches for guidelines across medline and embase returned 156 citations. 126 were excluded as irrelevant, leaving 32 abstracts for review. (Fig. 12) Of these, only one, mentioned previously, was found to have been developed systematically, and hence formally appraised (evidence table 18).[20]

Evidence Table 18: Damage control surgery (existing guidelines)

		Methodological assessment						
Biblio-graphic Citation	Summary	Scope and Purpose	Stake-holder Involve-ment	Rigour of Develop-ment	Clarity and Presen-tation	Applica-bility	Editorial Indepen-dence	Overall Assess-ment
Spahn et al (2007) [20]	This guideline recommends that "damage control surgery be employed in the severely injured patient presenting with deep haemorrhagic shock, signs of ongoing bleeding, and coagulopathy. Additional factors that should trigger a damage control approach are hypothermia, acidosis, inaccesible major anatomic injury, a need for time-consuming procedures, or concomitant major injury outside the abdomen." The authors accorde this recommendation a GRADE 1C.	89	50	71	75	11	100	+

Diagrammatic summary of evidence selection process

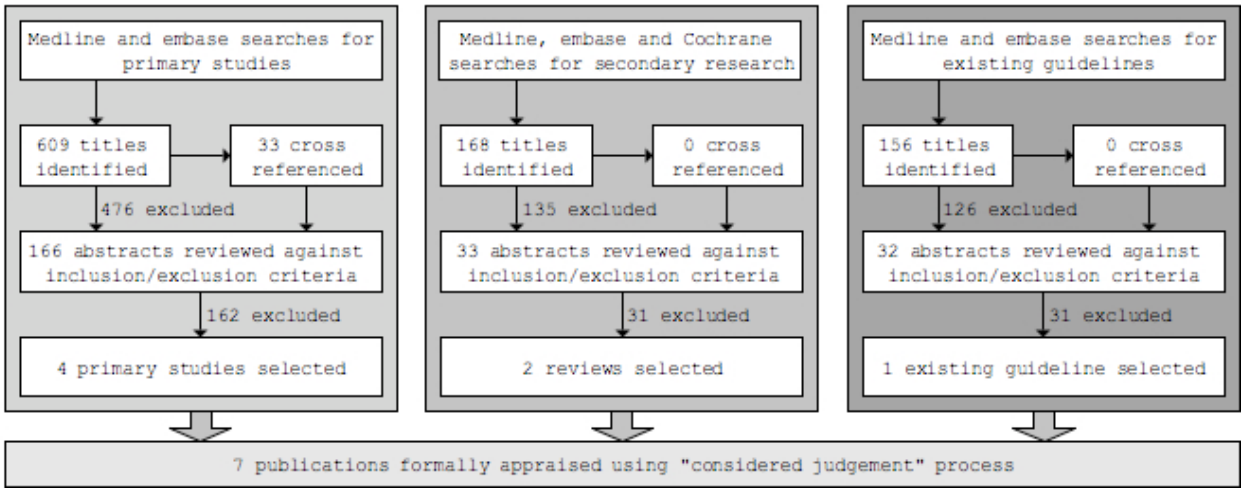

Fig 12. Diagrammatic summary of selection of literature relating to damage control surgery.

Appraisal

Volume of evidence: The volume of evidence for damage control surgery is poor. Despite a very large number of published primary studies and reviews, only very few are of acceptable quality. There are only three primary studies, incorporating only a few hundred patients, which compare damage control surgery with conventional definitive primary surgery. The vast majority of published primary studies are case series, of between three and several hundred patients, without comparison groups. Given the heterogeneity of injuries and severity, as well as surgical and non-surgical treatment, such studies are essentially meaningless. The only systematic review accurately reflects the quality of this evidence base. The large number of non-systematically developed review articles largely replicate the conclusions of previews reviews. *Applicability:*

None of the studies reviewed were performed within the context of haemostatic resuscitation, or aggressive hypothermia mitigation. The earliest of the better quality studies was published in 1983, the latest in 1993. It is reasonable to assume that many aspects of medical care, particularly in the fields of perioperative care and resuscitation, have changed dramatically since then. This is born out by Johnson et al's study.[165] *Consistency:* The largest of the three primary studies did not show a difference in mortality, and one of the two positive studies only showed a difference on subgroup analysis. *Clinical impact:* The clinical impact of damage control surgery, in terms of potential morbidity, mortality, and cost, is substantial. Nevertheless, its perceived benefits – in appropriately selected patients – may outweigh these considerations.

Evidence statement

Patients with severe intra-abdominal injuries – in particular those with profound haemorrhagic shock, an existing or developing coagulopathy, a need for time-consuming procedures, or concomitant major injury outside the abdomen – benefit from the use of damage control surgical techniques, which may include curtailment of the procedure by ligation of hollow viscus injuries or resection without anastomosis, ligation or shunting of vascular injuries, packing, and temporary abdominal closure.	2-

Future Research

There is an urgent need to better define the benefits of damage control surgery in the context of damage control resuscitation. Given the perceived benefits of the technique, withholding such therapy as part of a study may well be unethical. Although subject to a greater risk of confounding, historical or non-concurrent cohort studies represent the best compromise.

3.7 INDICATIONS

Damage control resuscitation consumes considerable resources in terms of blood products, theatre time, and critical care facilities. It is also associated with potential morbidity when applied injudiciously. Not every injured patient requires damage control resuscitation – in fact, only a small minority do, particularly in the civilian setting. When appropriate, however, damage control resuscitation must be applied expeditiously. Specific and practical indications for the initiation of damage control resuscitation would aid the appropriate and timely application of this strategy, and prevent the waste of precious resources in futile cases.

Key question

This section aims to answer the question “What are the indications for initiating damage control resuscitation?”

Outcome measures

Any parameters, clinical or laboratory, alone or in combination, which predict the need for damage control resuscitation.

Primary studies

```
Database: Ovid MEDLINE(R) <1950 to February Week 1 2009>
1     damage control resuscitation.mp. (17)
2     from 1 keep 3-4,8 (3)

Database: EMBASE <1980 to 2009 Week 07>
1     damage control resuscitation.mp. (10)
2     from 1 keep (0)

Inclusion criteria
1      Studies of diagnostic accuracy
2      Observational studies
3      Interventional studies

Exclusion criteria
1      Case reports
2      Case series
```

Systematic medline and embase searches using the term “damage control resuscitation” returned only 27 citations in total, which were therefore handsearched. 24 titles were excluded as irrelevant. Of the remaining three studies, one was a retrospective study of patients managed within the context of a damage control resuscitation type trauma exsanguination protocol, but did not take into account other components of the strategy, and did not specify indications.[61] The second was a study of the damage control resuscitation concept as a whole, as applied to military casualties having sustained peripheral vascular injuries, but only lists the indications as “life-threatening haemorrhage”.[8] The third was a retrospective study which evaluates two cohorts of military patients with vascular injuries, one managed with DCR, and one without.[9] It again does not specify indications beyond “life-threatening haemorrhage”. These studies were therefore disregarded.

Secondary research

```
Database: Ovid MEDLINE(R) <1950 to February Week 1 2009>
1     damage control resuscitation.mp. (17)
2     from 1 keep 6,10-15 (7)

Database: EMBASE <1980 to 2009 Week 07>
1     damage control resuscitation.mp. (10)
2     from 1 keep (5)

Inclusion criteria for abstract selection
1      Meta-analysis
2      Systematic review
```

```
Exclusion criteria for abstract selection
1      Non-systematic review
```

Of the 27 citations identified by the medline and embase searches noted, and an additional Cochrane library search, which returned no citations, 12 articles were reviewed. Although all relevant, none were based on a systematic review of the primary literature, and therefore excluded.

Existing guidelines

```
Database: Ovid MEDLINE(R) <1950 to February Week 1 2009>
1      damage control resuscitation.mp. (17)
2      from 1 keep (0)

Database: EMBASE <1980 to 2009 Week 07>
1      damage control resuscitation.mp. (10)
2      from 1 keep (0)

Inclusion criteria for abstract selection
1      Systematically developed guideline

Exclusion criteria for abstract selection
1      Non-systematically developed guidelines
2      Quasi-editorial guidelines
```

Medline and embase searches, as well as manual cross-referencing, returned no citations referring to existing guidelines.

Appraisal

There is insufficient evidence for a formal appraisal. This review aims to base its recommendations on methodologically rigorous research. Adherence to this principle has failed to reveal any studies which meet the inclusion criteria. This does not imply that there are no indications, or indeed defined indications, for the application of damage control resuscitation, only that these indications are not evidence-based. There is a considerable body of literature on the subject, and most authors agree that trauma patients with exsanguinating haemorrhage, those with an existing coagulopathy, and those at high risk of coagulopathy, benefit from damage control resuscitation.[3][7][15][16][31] The indications are therefore clinical, derived from data and experience extrapolated from multiple sources, amounting to expert opinion only. However, in the correct setting, applied by a suitably experienced practitioner, they may be clinically relevant and useful. Advances in the rapid diagnosis of traumatic coagulopathy will hopefully permit a more evidence-based approach to decisionmaking in the future.

Evidence statement

There is insufficient evidence for an evidence statement.

4.

Discussion

4.1 SUMMARY OF EVIDENCE

This section summarises and contextualises the findings of the systematic review.

4.1.1 Fresh frozen plasma

In patients with traumatic haemorrhage predicted to require massive transfusion (defined as more than 8-10 units of packed red blood cells in the first 24 hours after injury), a high ratio of fresh frozen plasma to packed red blood cells is associated with decreased mortality.	2+

Greater appreciation of the importance of traumatic coagulopathy has prompted studies into the role of aggressive clotting factor replacement with fresh frozen plasma. However, prospective or indeed randomised evidence is still lacking, and the precise indications for the initiation of this strategy also remain undefined (see also section 4.1.10), as study patients were enrolled retrospectively.

A fresh frozen plasma to packed red blood cell ratio of approximately 1:1 units appears to be optimal, although this evidence is extrapolated from studies which retrospectively stratified intervention groups for survival analysis, rather than dose-finding studies.	2+

Studying the effects of the use of predefined ratios of fresh frozen plasma and packed red cells is beset by practical difficulties: In order to administer fresh frozen plasma from the outset of resuscitation, pre-thawed plasma must be available. Unless the volume of trauma is very high, this will lead to considerable waste. At present, few civilian trauma centres reach this threshold, marking an important differences between civilian and deployed military practice. If FFP is only defrosted on demand, several units of packed red cells may have already been given before plasma is commenced, resulting in a “catch-up” situation, if a ratio of 1:1 is to be attained. Furthermore, survivors may be self-selecting in this situation: Patients who live long enough to get FFP are more likely to attain the 1:1 ratio. The timing of fresh frozen plasma administration is thus an important confounder which has not yet been addressed, and which requires a prospective study to evaluate.

It is also not known whether the benefits of aggressive fresh frozen plasma use could equally apply to patients needing less than 10 units of packed red blood cells. It is likely that the benefits

of such a strategy, if they are indeed real, are less pronounced in patients requiring smaller volume transfusions. None of the studies conducted so far have adequately delineated the side-effect profile of aggressive fresh frozen plasma use, and there is ongoing concern regarding the side effects of this strategy, and in particular whether it might result in a higher incidence of ARDS.

The diagnosis of traumatic coagulopathy is clinical. Clotting assays such as prothrombin time and partial thromboplastin time take time to process, and lack validity in the trauma setting. In the exsanguinating trauma patient, haemostatic resuscitation should be initiated without awaiting the results of such assays. There is, however, also a theoretical concern regarding the administration of large amounts of plasma to patients who are not coagulopathic, or who may even be hypercoagulable, in which cases thrombotic complications may ensue. This has not been shown to be the case until now, but has also not been adequately investigated. The more widespread use of thromboelastography, or rotational thromboelastometry – particularly as a point-of-care test – might allow more rapid and more precise identification of coagulation defects.

In summary, although there is reasonable evidence that a strategy of transfusing fresh frozen plasma and packed cells in a 1:1 ratio is associated with improved outcome in coagulopathic trauma patients, better quality evidence is needed to confirm the benefits and define the place of this strategy.

4.1.2 Platelets

In patients with traumatic haemorrhage predicted to require massive transfusion (defined as more than 8-10 units of packed red blood cells in the first 24 hours after injury), a high ratio of units of platelets to packed red blood cells is associated with decreased mortality. A ratio of at least 1 (pooled) unit of platelets to 5 units of packed red blood cells appears to be optimal, although this evidence is extrapolated from studies which retrospectively stratified intervention groups for survival analysis.	2-

The evidence base for the liberal use of platelets is even more limited than for fresh frozen plasma. Furthermore, as with fresh frozen plasma, the precise indications for the initiation of this strategy remain undefined (see also section 4.1.10), and it is not known whether the benefits of aggressive platelet use could also apply to patients needing less than 10 units of packed red blood cells. The same concerns regarding the side effects of this transfusion strategy also apply.

4.1.3 Recombinant factor VIIa

Recombinant factor VIIa reduces transfusion needs in blunt trauma patients requiring massive transfusion (defined as more than 8 units of packed red blood cells). The effect of recombinant factor VIIa on mortality/survival in this setting is not known.	1-
Recombinant factor VIIa may also reduce transfusion needs in penetrating trauma patients requiring massive transfusion (defined as more than 8 units of packed red blood cells), but the evidence in this setting is less clear. As in blunt trauma, the effect of recombinant factor VIIa on mortality/survival in this setting is also not known.	1-

Recombinant factor VIIa is one of the best researched therapies in trauma care, and one of the few treatments to have been tested in randomised controlled trials. However, these trials [99] were not powered to detect differences in mortality, or complications, and had methodological shortcomings. The multi-national, multi-centre design was very complex, and probably contributed to a substantial number of patients being lost to follow-up. Treatment other than the administration of rFVIIa was not standardised. Several authorities have suggested that the first dose of rFVIIa given after 8 units of transfused packed red blood cells may have been "too little, too late". Concealment of allocation was unclear, and the statistical analysis was opaque. Most importantly, these trials were conducted prior to the acceptance of the "1:1" principles described above (see sections 4.1.1 and 4.1.2). The utility of recombinant factor VIIa within the context of haemostatic resuscitation, and the time when treatment with recombinant factor VIIa should be initiated, is not known. Recombinant activated factor VIIa may be required less frequently when this resuscitation strategy is employed. This question could only be answered by a further trial. Given the substantial cost of a single dose of recombinant factor VIIa, a further study warrants serious consideration. Until such time, the use of rfVIIa is justified in cases in whom contemporary method haemostatic resuscitation have failed to arrest the development of coagulopathy, in both blunt and penetrating trauma.

4.1.4 Cryoprecipitate

The use of cryoprecipitate in exsanguinating haemorrhage is founded on reasonable scientific principles, but its use in trauma patients is largely based on studies of poor methodology, and extrapolated data. Cryoprecipitate should be considered when hypofibrinogenaemia has been confirmed, or when traumatic coagulopathy, whether diagnosed clinically or by assay, is not responding to other methods of haemostatic resuscitation.	3

Concerns about patient exposure to large numbers of donors, and associated risks of blood borne virus transmission, limit the use of cryoprecipitate to situations where more conventional treatment has failed. Novel treatments such as single-factor concentrates (for example, fibrinogen) and complexes (such as prothrombin complex concentrate) avoid some of these problems, and are therefore attractive substitutes, but presently lack an evidence base in the context of trauma care.

4.1.5 Tranexamic acid

Appreciation of the contribution of hyperfibrinolysis to the acute coagulopathy of trauma shock has renewed interest in the role of antifibrinolytic agents in trauma. Tranexamic acid has been shown to reduce blood loss in elective surgery, but there is insufficient evidence from randomised trials of antifibrinolytic agents in trauma patients to either support or refute a clinically important treatment effect. However, given the proven efficacy and effectiveness of antifibrinolytics in reducing blood loss in elective surgery, and the lack of serious side effects, many authorities recommend the administration of tranexamic acid to haemorrhaging trauma patients, until further evidence becomes available. As this practice is based purely on expert opinion, rather than evidence, a formal evidence statement is not justifiable. The efficacy of tranexamic acid in this setting is the subject of an ongoing, multinational trial (CRASH2, Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage).

Aprotinin, another antifibrinolytic agent, was widely used, particularly in cardiac surgery, until a few years ago, but recently had its licence withdrawn because of concerns about cardiac and renal complications.

The more widespread use of thromboelastography, which permits the identification of a hyperfibrinolytic component to haemostatic compromise, would allow more targeted treatment.

4.1.6 Permissive hypotension

Permissive hypotension is not a new concept, but has gained a new "lease of life" as part of damage control resuscitation, particularly in the military setting. The three trials of permissive hypotension conducted over the last 15 years all have significant methodological limitations. Bickell et al's study was the only one to show a difference in mortality, but was not randomised, and conducted in very specific circumstances: The geographical area from which patients were recruited was small, all had penetrating torso trauma, and all were young.[121] Turner et al's cluster-randomised trial suffered from the inclusion of large numbers of patients with minor injuries and numerous protocol violations.[122] Dutton et al's study failed to achieve the proposed methodology and was underpowered.[123]

There is no new evidence to suggest that pre-hospital intravenous fluid resuscitation prior to control of bleeding is beneficial. There is, however, limited evidence to suggest that fluid resuscitation may be harmful, and that patients with penetrating injuries in particular may have better outcomes when fluids are withheld until surgical control of haemorrhage has been obtained.	1-

Few would argue against replacing lost intravascular volume in patients with controlled or self-limiting haemorrhage. In contrast, in patients with uncontrolled haemorrhage, particularly in the context of penetrating torso trauma, a strategy of permissive hypotension, together with rapid control of haemorrhage, may be more appropriate. Distinguishing between these two groups can be difficult, and take time.

It is probable that there is a critical period during which suboptimal end-organ perfusion is tolerated, but beyond which irreversible anatomical and physiological changes manifest. The duration of this period remains to be defined.

It is conceivable that permissive hypotension is more applicable to the management of penetrating injuries than blunt trauma. The management of polytrauma patients with head injuries requires special mention. The importance of maintaining cerebral perfusion pressure is well recognised, and permissive hypotension may be contraindicated in this setting. Conversely, in an exsanguinating patient with a coexisting head injury, control of haemorrhage is arguably still the higher priority, and may be the best way of restoring cerebral perfusion.

Despite a lack of evidence, clinical practice has evolved to a much more judicious administration of intravenous fluids. In recognition of the unique challenges posed by combat casualty

resuscitation, permissive hypotension has been firmly incorporated into military medical doctrine, and is now also being endorsed by several civilian organisations. [128][172] [173][174][175] The forthcoming eighth edition of the Advanced Trauma Life Support programme also departs from previous guidance by emphasising the need to balance the risks of precipitating further bleeding against the adequacy of organ perfusion, and accepting a lower than normal blood pressure until surgical control of haemorrhage has been obtained.

There is an urgent need for more studies of fluid resuscitation in clearly defined populations, including those with head injuries, and studies to define the time period during which suboptimal end-organ perfusion is tolerated and reversible.

4.1.7 Tris-hydroxymethyl aminomethane (THAM)

THAM is a buffering agent which has been used in the treatment of respiratory failure, head injury management, diabetic ketoacidosis and poisoning. Unlike bicarbonate, which relies on the respiratory system for the elimination of carbon dioxide, protonated THAM is excreted renally. Acidaemia in trauma is almost invariably the consequence of hypoperfusion, and should ideally be corrected by restoring oxygen delivery, but offsetting its effects on coagulation and myocardial contractility by pharmacological modulation is attractive. Several authors have alluded to the potential usefulness of THAM in trauma patients, but there is no direct evidence to support its use in trauma patients. Studies are needed to confirm efficacy and define indications for treatment with THAM in trauma patients.

4.1.8 Hypothermia

Hypothermia in trauma patients is associated with increased mortality. Reversal of hypothermia is associated with improved survival. Hypothermia in trauma patients should therefore be prevented whenever possible, and aggressively treated when present.	2+

There is very little evidence to support the use of any one device, or combination of devices, over another. Although there are numerous comparisons, very few were conducted in the trauma setting. The mechanisms underlying the development of hypothermia may differ between trauma and non-trauma patients, and because surgical intervention in trauma patients often requires wide access. One study has shown that prewarmed blankets are as efficacious, but less cumbersome, than forced air devices in *preventing* hypothermia in trauma patients admitted with normothermia. This study was confined to patients with minor or moderate trauma, and its

findings are thus not applicable to other populations, or the *treatment* of hypothermia. Forced air devices are effective but impractical in the trauma setting, because they limit access. They are, however, useful in the pre-operative and, particularly, post-operative phases of care. Although there is no direct evidence to support their use, electrical warming mattresses are the most practical devices. These devices are effective and do not compromise access.

There is no evidence to support the use of extracorporeal warming techniques, such as cardiopulmonary or passive arteriovenous bypass, as sometimes used for the treatment of severe hypothermia due to prolonged exposure or drowning, for the treatment of trauma-associated hypothermia. These systems are cumbersome to set up and use, are associated with risks such as thrombosis and haemorrhage due to decannulation, and may be contraindicated if anticoagulation is required. The use of cavity rewarming techniques such as peritoneal or pleural lavage is also impractical, and there is no evidence of its utility in trauma.	2-

4.1.9 Damage control surgery

Damage control surgery is regarded as one of the key advances in trauma management of the last 20 years. It has become both a cornerstone and hallmark of trauma surgery, and it is thus surprising how little evidence there is to support the concept. This is probably the consequence of both less exacting proofs of efficacy required when the technique was introduced, and the usual difficulties encountered when trying to conduct studies on severely injured patients.

Lack of evidence for a treatment does not equate to ineffectiveness. There are many treatments, particularly surgical, which have never been subjected to formal evaluation. Indeed, attempting to prove the efficacy of damage control surgery (and resuscitation) by means of comparative studies might expose patients to unacceptable risks, and be considered unethical. The scientific rationale for damage control surgery is compelling, and there is a large amount of indirect and circumstantial evidence to support its use. Few trauma surgeons would argue against employing damage control surgical techniques in the correct setting.

Patients with severe intra-abdominal injuries – in particular those with profound haemorrhagic shock, an existing or developing coagulopathy, a need for time-consuming procedures, or concomitant major injury outside the abdomen – benefit from the use of damage control surgical techniques, which may include curtailment of the procedure by ligation of hollow viscus injuries or resection without anastomosis, ligation or shunting of vascular injuries, packing, and temporary abdominal closure.	2-

Damage control surgery carries with it significant risks in terms of morbidity – such as sepsis related to abdominal packing, inability to secondarily close the abdomen or reconstruct the abdominal wall, enterocutaneous fistulation, to name a few – and even mortality. It is likely that its benefits are most evident in patients with severe injuries. In this setting, the perceived benefits of the strategy may well be amplified by the use of other damage control resuscitation strategies, such as haemostatic resuscitation and temperature maintenance. Damage control surgery should therefore not be employed outwith the context of damage control resuscitation.

4.1.10 Indications for initiating damage control resuscitation

The indications for damage control resuscitation remain poorly defined. This is problematic both in terms of appropriate selection of patients, and the reporting and comparison of results of treatment. There is a substantial body of literature on transfusion practice, and massive transfusion and trauma exsanguination protocols, but studies are either not evidence-based, predate recent clinical developments in coagulopathy management, are restricted to haematological aspects of management, or not specifically aimed at trauma patients. Some of the recent studies of predefined plasma to packed cell ratios used the inclusion criterion “massive transfusion” (defined as more than 8 or 10 units of packed cells transfused within the first 24 hours after injury), but this was applied retrospectively, and is obviously of no use to the clinician faced with a trauma patient who has just arrived in the emergency department. Equally, there are many articles regarding parameters or combinations of parameters – such as temperature, base excess, or prothrombin time – which are said to indicate the need for damage control rather than definitive primary surgery, but these were again never formally tested, and also predate the introduction of haemostatic resuscitation.

In summary, the indications for damage control resuscitation remain imprecise. Several recent publications, many written by experts in the field, gloss over this important aspect, referring to “patients with exsanguinating haemorrhage” or “patients at risk of coagulopathy”.[3][7] This is unsatisfactory both in terms of resource utilisation and potential morbidity: Many less severely

injured trauma patients are hyper- rather than hypocoagulable, and aggressive administration of fresh frozen plasma could conceivably be harmful in this setting. However, until more objective parameters for diagnosis and selection are developed, pattern recognition by an experienced physician remains the only "test" available.

4.2 VALIDITY, LIMITATIONS AND APPLICABILITY

The objectives of this dissertation (section 1.2) was "to conduct a systematic review of the evidence for damage control resuscitation". Has this objectives been achieved?

4.2.1 Validity

Section 1.4 defined a systematic review as an efficient scientific technique to identify and summarise evidence on the effectiveness of interventions, and identified its characteristics as an explicit search strategy, selection of literature according to defined inclusion and exclusion criteria, and evaluation against consistent standards.[20][22]

The search strategies employed in this dissertation are explicit, and in all likelihood sufficiently inclusive to identify the vast majority of publications relating to each of the key questions, although this latter fact is impossible to prove. Articles were furthermore selected according to defined inclusion and exclusion criteria. The trauma literature is unfortunately replete with methodologically inferior studies, and the selection process was specifically designed to eliminate such work. In particular, primary studies such as case reports and case series without control groups were excluded. Non-systematic reviews and quasi-editorial guidelines, representing a very substantial proportion of the literature, were treated as "expert opinion" and also disregarded. This highly selective approach is not without problems, as there are some treatments which have a limited or even no evidence base. In contrast, some of the more recent innovations, in particular haemostatic resuscitation, are characterised by a much better scientific foundation.

The articles selected for incorporation into the systematic review were furthermore evaluated against consistent and accepted standards. This work therefore meets all the criteria of a systematic review.

4.2.2 Limitations

The principal limitation of this work in terms of its validity is that it was produced by a single author. Both selection bias, during the identification of potentially relevant publication, and

appraisal bias, during the analysis of selected evidence, is greatly reduced by multiple assessors reaching a consensus. Although such a process increases validity, it is not appropriate – or indeed practical – for a doctoral thesis, and was therefore omitted.

4.2.3 Applicability

Despite the limitations listed in section 4.2.2, this dissertation has succeeded in systematically and comprehensively reviewing the available evidence for the components of the damage control resuscitation strategy. Although some of the included studies were conducted in the military setting, the conclusions are broadly applicable to civilian trauma management in the context of a European or North American trauma centre.

4.3 CONCLUSION

The management of major trauma has undergone dramatic changes, which have been drawn together into the damage control resuscitation concept. Haemostatic resuscitation, hypothermia management, hypotensive resuscitation, and damage control surgery have been amalgamated into a coherent management strategy, which has revolutionised the care of the injured.

Those with more than just a passing interest in the history of trauma will recognise that many of the component strategies of damage control resuscitation are not new, but merely developments of existing concepts. Irrespective of origin or originality, contemporary medical practice demands that new therapies are supported by scientific evidence. Trauma care has long suffered from a lack of such evidence. This is a direct result of the difficulty of conducting interventional studies on patients with life-threatening injuries: Except in the very largest centres, the numbers of patients admitted with major trauma are relatively small, and trauma is a heterogeneous disease: Injury patterns and severity vary, and are difficult to control for. Resuscitation, surgical treatment, and postoperative care are difficult to standardise. The selection of outcome measures is also problematic: Mortality is easily assessed, and always clinically significant, but may not be appropriate, or require very large studies to reach statistical significance. Lastly, patient consent, an essential safeguard of ethical research practice, is often difficult or even impossible to obtain from patients requiring emergency treatment.

Although these difficulties are real, they should not detract from the need to demonstrate that novel treatments are effective. Proving the effectiveness of a strategy such as damage control resuscitation is difficult, and should ideally take place at several levels, confirming both the effectiveness of the constituent components, and the strategy as a whole.

This dissertation has distilled the evidence, and in some cases, lack of evidence, for the components of damage control resuscitation. It cannot, and never set out to, prove the effectiveness of damage control resuscitation as a whole. Indeed, the complex issues – methodological and ethical – that a study attempting to demonstrate its efficacy would throw up make it highly unlikely that such an investigation will ever take place.

Fortunately, there is indirect evidence that damage control resuscitation is effective. Given its origins, it is fitting that this evidence should come from military practice, which has been meticulously evaluated for many years. The lethality of war wounds sustained by US servicemen decreased from 30% in the second World War (1939-1945), to 25% during the Korean War (1950-1953), but then remained at 24% during the Vietnam War (1961-1973), and even the first Gulf War (1990-1991), some thirty years later. Since 2001, however, despite increases in the wounding potential of modern weapon systems, less than 10% of US servicemen wounded in Iraq and Afghanistan have died.[1][2][10] Although the precise role of medical care, and damage control resuscitation in particular, is impossible to ascertain, it has almost certainly contributed to this remarkable reduction in combat-related mortality.[1] The successful development and implementation of the damage control resuscitation concept by the military – in an operational setting – is a remarkable achievement. The lessons learnt are now redefining the care of the most severely injured patients in civilian practice.

5.

Abstract

(English)

Background: Damage control resuscitation is a novel strategy for the management of the exsanguinating trauma patient. It is a development of the damage control surgery concept, with emphasis on the integration of resuscitation and surgery, and the aggressive management of traumatic coagulopathy. Although pioneered by military surgeons, many aspects of damage control resuscitation are equally applicable to the management of civilian trauma, but awareness outside specialist circles is limited. This is at least in part related to the lack of a precise definition, and the rapid and continuing evolution of the strategy.

Objectives: 1. To define the components of damage control resuscitation. **2.** To conduct a systematic review of the evidence for damage control resuscitation.

Methods: Systematic review of literature.

Results: Damage control resuscitation encompasses haemostatic resuscitation, hypotensive resuscitation, hypothermia and acidaemia management and damage control surgery. Systematic review produced the following conclusions: In patients with traumatic haemorrhage predicted to require massive transfusion, a high ratio of fresh frozen plasma to packed red blood cells is associated with decreased mortality. (Evidence level: 2+) A ratio of approximately 1:1 units appears to be optimal, although this evidence is extrapolated from studies which retrospectively stratified intervention groups for survival analysis, rather than dose-finding studies. (2+) In patients with traumatic haemorrhage predicted to require massive transfusion, a high ratio of units of platelets to packed red blood cells is also associated with decreased mortality. A ratio of at least 1 (pooled) unit of platelets to 5 units of packed red blood cells appears to be optimal, although this evidence is again extrapolated. (2-) Recombinant factor VIIa reduces transfusion needs in blunt trauma patients requiring massive transfusion. The effect of recombinant factor VIIa on mortality in this setting is not known. (1-) Recombinant factor VIIa may also reduce transfusion needs in penetrating trauma patients requiring massive transfusion, but the evidence is less clear. As in blunt trauma, the effect on mortality in this setting is also not known. (1-) The use of cryoprecipitate in exsanguinating haemorrhage is founded on reasonable scientific principles, but its use in trauma patients is largely based on studies of poor methodology, and extrapolated data. Cryoprecipitate should be considered when hypofibrinogenaemia has been confirmed, or when traumatic coagulopathy is not responding to other methods of haemostatic resuscitation. (3) Although conceptually attractive, associated with few complications, and frequently recommended, there is no evidence for the use of antifibrinolytics in the trauma setting. There is no new evidence to suggest that pre-operative intravenous fluid resuscitation prior to control of bleeding is beneficial. There is, however, limited evidence to suggest that fluid

resuscitation may be harmful, and that patients with penetrating injuries in particular may have better outcomes when fluids are withheld until surgical control of haemorrhage has been obtained. (1-) There is no evidence to support the use of tris-hydroxymethyl aminomethane (THAM) in trauma patients, although in theory appealing. Hypothermia in trauma patients is associated with increased mortality, and should be prevented whenever possible, and aggressively treated when present. (2+) There is no evidence to support the use of extracorporeal warming techniques. (2-) Patients with severe intra-abdominal injuries – in particular those with profound haemorrhagic shock, an existing or developing coagulopathy, a need for time-consuming procedures, or concomitant major injury outside the abdomen – benefit from the use of damage control surgical techniques, which may include curtailment of the procedure by ligation of hollow viscus injuries or resection without anastomosis, ligation or shunting of vascular injuries, packing, and temporary abdominal closure. (2-) The indications for damage control resuscitation remain poorly defined. This applies both in general, and for specific components, such as when resuscitation with predefined blood product ratios should be initiated, or at what stage recombinant factor VIIa should be utilised. Existing criteria are largely based on expert opinion.

Discussion: Damage control resuscitation is a composite, multidisciplinary strategy which integrates haemostatic resuscitation, hypotensive resuscitation, hypothermia management, and damage control surgery. Hypotensive resuscitation and damage control surgery are not new concepts, but have been incorporated into an effective management paradigm. Greater appreciation of the importance of traumatic coagulopathy, and its manipulation through haemostatic resuscitation, has led to an explosion of interest in clotting factor and platelet replacement. The resulting resuscitation strategies with predefined ratios of blood products, and avoidance of synthetic fluids, together with the modulation of fibrinolysis, are an exciting development. Although much work remains to be done, these novel treatments, in combination with more established techniques, are revolutionising major trauma resuscitation. This systematic review should assist clinicians in applying damage control resuscitation principles, and maximising their patients' survival.

6.

Zusammenfassung

(Deutsch)

Hintergrund: Damage Control Resuscitation (DCR) ist eine innovative Strategie zur Behandlung von Traumapatienten mit hohem Blutverlust. Sie ist eine Weiterentwicklung des chirurgischen Damage Control-Konzepts mit dem Schwerpunkt einer Kombination aus Reanimations- und chirurgischer Therapie sowie der konsequenten Behandlung der traumatischen Koagulopathie. Die DCR wurde ursprünglich von Militärchirurgen eingeführt, große Teile sind jedoch auch in der Therapie ziviler Verletzter anwendbar. Dass die Kenntnis hiervon bisher auf Spezialisten begrenzt war, liegt zum einem am Fehlen einer präzisen Definition, zum andern an der rapiden Weiterentwicklung der Behandlungsstrategien.

Ziele: Es gilt erstens, die einzelnen Komponenten der Damage Control Resuscitation zu definieren, zweitens, eine systematische Sichtung der Evidenzbasierung der DCR durchzuführen.

Methode: Systematische Literaturrecherche unter Anwendung von gängigen Evaluierungsmethoden.

Ergebnisse: Damage Control Resuscitation ist die (lebensrettende) Behandlung von Gerinnungsstörung, Hypothermie, Acidose und die kontrollierte Toleranz einer verminderten Perfusion, in Verbindung mit Damage Control-Chirurgie. Die systematische Analyse ergab folgende Resultate: die Mortalität von Patienten mit traumatischen Blutungen, die massive Transfusionen benötigen, wird durch ein 1:1 Verhältnis von Gefrorenem Frischplasma zu Erythrocytenkonzentraten deutlich gesenkt. (Evidenzgrad 2+). Diese Evidenz ist allerdings aus retrospektiven Studien extrapoliert, die sich weniger mit der Dosierung als vielmehr mit der Festlegung von Interventionsgruppen zur Beurteilung der Überlebensrate befassten.(2+) Auch ein hoher Anteil von Thrombocyten – im Verhältnis zu Erythrocyten – Konzentraten lässt eine verminderte Mortalität bei polytransfundierten Patienten erwarten. Eine Relation von wenigstens einem Pool- Thrombocyten-Konzentrat zu fünf Erythrocyten-Konzentraten scheint optimal, wobei auch diese Schlussfolgerung extrapoliert ist. (2-) Recombinanter Faktor VIIa vermindert die Anzahl der erforderlichen Transfusionen bei stumpfem Trauma, jedoch ist ein Effekt von Faktor VIIa auf die Mortalität nicht bekannt. (1-) Faktor VIIa reduziert möglicherweise auch die notwendige Transfusionsmenge bei Patienten mit penetrierenden Verletzungen. Dieser Zusammenhang ist indes nicht klar erwiesen, auch der Effekt auf die Mortalität ist – wie beim stumpfen Trauma – nicht bekannt. (1-)

Der Gebrauch von Kryopraezipitaten bei Patienten mit nicht-traumatischen lebensbedrohlichen Blutungen gründet sich auf fundierte wissenschaftliche Prinzipien; bei Traumapatienten basiert er aber auf Studien, deren Methode und Daten fragwürdig sind. Der Gebrauch von

Kryopraezipitaten sollte erwogen werden, wenn eine Hypofibrinogenaemie nachgewiesen ist oder wenn die traumatische Koagulopathie auf andere Therapieversuche nicht reagiert. (3) Obwohl häufig empfohlen, vom Ansatz her attraktiv und mit geringen Komplikationen belastet, ist der Nutzen einer Antifibrinolytikabehandlung in der Traumaversorgung nicht evident. Auch präoperative Flüssigkeitsinfusionen – ehe die Blutung beherrscht werden kann – erscheinen fragwürdig. Es gibt Untersuchungen darüber, dass Flüssigkeitszufuhr schädlich sein kann und dass bei Patienten mit penetrierenden Verletzungen zunächst eine chirurgische Kontrolle der Blutung erreicht werden sollte. (1-) Keine Evidenzbasis findet sich für die Anwendung von Trishydroxymethylaminomethan (THAM) bei Traumapatienten, obwohl der theoretische Ansatz für eine solche reizvoll ist. Hypothermie ist bei Traumapatienten mit erhöhter Mortalität verbunden, muss vermieden oder – wenn eingetreten – aktiv behandelt werden. (2+) Für die Anwendung extrakorporaler Aufwärmtechniken gibt es keine Rechtfertigung. (2-) Patienten mit schweren intraabdominalen Verletzungen, insbesondere solche mit haemorrhagischem Schock, einer vorhandenen oder sich entwickelnden Koagulopathie, folgenden langwierigen Operationen oder mit zusätzlichen grösseren Verletzungen außerhalb des Abdomens profitieren von der Anwendung chirurgischer Damage Control-Techniken. Diese können in einer zeitlichen Begrenzung der Operation bestehen, zum Beispiel durch Verschluss von Hohlorganen oder Resektion ohne Anastomose, in Ligatur oder Überbrückung (shunting) von Gefässverletzungen, in „packing“ und provisorischem Abdominalverschluss. (2-) Die Indikationen für Damage Control Resuscitation sind weiterhin unzureichend definiert. Dies gilt sowohl in allgemeiner Hinsicht als auch im Hinblick auf spezifische Fragestellungen: wann etwa soll eine lebensrettende Behandlung mit festgelegten Mengen von Blutersatzprodukten begonnen werden oder in welchem Stadium Faktor VIIa zum Einsatz kommen. Vorhandene Kriterien basieren fast ausschließlich auf persönlichen Erfahrungen.

Diskussion: Damage Control Resuscitation ist eine komplexe, multidisziplinäre Strategie, die lebensrettende Haemostase-, Hypothermiebehandlung, Hypotensions-Toleranz sowie Damage Control Chirurgie beinhaltet. Toleranz einer verminderten Perfusion und DC-Chirurgie sind keine Neuerungen an sich, sie werden jedoch in ein effektives Therapieschema eingebettet. Zunehmende Berücksichtigung der traumatischen Koagulopathie und ihre Behandlung haben zu einer Ausweitung des Interesses an Gerinnungsfaktoren und Thrombocytenersatz geführt. Die resultierenden lebenserhaltenden Maßnahmen mit vorgegebenen Mengen von Blutersatzprodukten, bei Vermeidung synthetischer Flüssigkeiten, sind in Verbindung mit der vorsichtigen Beeinflussung der Fibrinolyse eine interessante Entwicklung. Obwohl die

Forschungsbasis noch erweitert werden muss, bereichern diese neuen Behandlungsmethoden in Verbindung mit bewährten Techniken die Lebensrettungsmaßnahmen bei Schwerverletzten schon heute. Der vorliegende systematische Überblick sollte es Klinikern ermöglichen, DCR-Prinzipien anzuwenden und die Überlebenschancen ihrer Patienten zu vergrößern.

7.

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8.

Declaration/Erklärung

“Ich, Jan Olaf Jansen, erkläre, dass ich die vorgelegte Dissertation mit dem Thema: ‘Damage Control Resuscitation: Systematic Review’ selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.“

09.05.2009 J. Jansen

9.

Curriculum Vitae/Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

10.

Publications/Publikationsliste

BOOK CHAPTERS/ BUCHKAPITEL

Jansen JO, Loudon MA. Investigation and management of blunt abdominal trauma. *In:* Johnson C, Taylor I. Recent Advances in Surgery 32. London. 2009.

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11.

Dedication

I would like to thank Priv.-Doz. Dr. med. Andreas Eisenschenk for his supervision, my parents for their support, and – most importantly – my wife and son for their understanding.