Title

The clinical effectiveness and cost-effectiveness of pre-hospital intravenous fluids in trauma patients

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ABOUT "HOME UNIT"

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produces rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands NHS and the NCCHTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

CONTRIBUTIONS OF AUTHORS

Janine Dretzke was the lead reviewer, she worked on the protocol, identification of studies, quality assessment, data extraction and wrote the methods and results section of the report. She helped write the discussion and conclusions. She read and approved the final draft.

Josie Sandercock gave methodological advice, and contributed to the protocol, quality assessment and data extraction. She helped write the discussion and conclusions. She read and approved the final draft.

Sue Bayliss is an information specialist and developed and ran all the electronic searches. She read and approved the final draft.

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The contents of the report remain the responsibility of the authors.

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Description of proposed service

The focus of this report was to determine whether pre-hospital intravenous fluid replacement, compared to no intravenous fluid replacement or delayed fluid replacement, should be undertaken in trauma patients who have haemorrhage-induced hypotension due to trauma. The evidence surrounding the effects of a potential delay to definitive treatment and the choice of fluid was also considered. Trauma patients with head injuries were not included.

Epidemiology and background

Trauma is an important cause of death and disability in the UK, with road traffic accidents causing a substantial number of injuries. There is no comprehensive audit data on the use of pre-hospital IV fluids available. Figures from previous research and some audit data suggest that between 5% and 18% of trauma patients receive fluids (generally crystalloids), representing 9-65 patients/year/100,000 population.

The term 'shock' is used to describe circulatory failure leading to inadequate perfusion and oxygenation of the tissues. This can cause permanent damage to essential organs and may result in multiple organ failure and death. One cause of shock is bleeding (hypovolaemic shock). Traditionally, the management of bleeding trauma patients has included early rapid fluid replacement by paramedics on scene, on the basis that increasing the circulating volume and blood pressure will help to maintain vital organ perfusion (supported by early animal studies). In the 1980s, however, it was increasingly suggested (partly on the basis of observational studies) that delaying definitive treatment may be harmful and there was a new emphasis on the prevention of on-scene delays. Newer animal models of uncontrolled haemorrhage indicated that fluid repacement itself may be harmful and it was argued that, by restoring blood pressure with fluids, the risk of blood loss was increased through the dilution of clotting factors and the mechanical disruption of clots. Whilst a policy of transferring trauma patients to hospital as quickly as possible with minimal on-scene delay is now widely supported in the UK, there is still a lack of consensus about whether fluid resuscitation *per se* is beneficial or harmful.

Current service provision

Ambulance crews consist of one driver and one attendant. They can be emergency medical technicians (trained in basic life support) or paramedics (who have additional skills in advanced life support skills). Only paramedics can administer IV fluids. Current policy is for ambulance crews to include one paramedic.

Current Ambulance Service policies for IV fluid resusciation are set out in the 2002 JRCALC guidelines. These are consistent with the Consensus Statement Guidelines of the Royal College of Surgeons of Edinburgh (except that for hypovolaemia they recommend an initial rapid infusion of 500ml of crystalloid to achieve a peripheral or carotid pulse rather than 250ml). Both recommend avoidance of on-scene delay and represent a shift to a more cautious (hypotensive) fluid resuscitation policy than previously advocated.

It is not clear to what extent current guidelines are being adhered to but there are suggestions that there may still be avoidable on-scene delay.

Number of studies
Evidence was available in the form of four randomised controlled trials investigating aspects of fluid resuscitation protocols (delay, volume, speed) and a previous Cochrane systematic review reporting on the timing and volume of fluid resuscitation. Observational studies listed in the Consensus Statement were also critically appraised.

We found two systematic reviews on ALS versus BLS and ten systematic reviews comparing different types of fluids.

We searched for, but did not find, systematic reviews specifically addressing the following questions: effect of fluid replacement for different types of injuries (e.g. blunt vs penetrating); effect of fluid replacement in paediatric trauma patients; ability of paramedics to accurately diagnose hypovolaemia at the scene; effects of naturally occurring physiological shock mechanisms and interaction with fluid resuscitation.

Quality of studies and direction of evidence
The observational studies were particularly inconclusive as regards use of fluids because of extensive uncontrolled confounding due to their design and analysis. Three of the four RCTs were poorly designed and/or conducted. One good quality RCT suggested that IV fluids may be harmful in patients with penetrating injuries. No pathophysiological reasons or empirical evidence was found that would suggest that the intervention is likely to be more or less harmful in blunt than in penetrating trauma.

There was some, potentially confounded, evidence from observational studies to suggested that a delay to definitive treatment may be harmful.

No reliable evidence was found from systematic reviews to suggest that a particular type of fluid is more beneficial over another type of fluid in trauma patients, although there was a trend favouring crystalloids over colloids.

Costs
The relative cost of using IV fluids versus not using them is very similar: the giving sets and fluids currently used are extremely cheap; not using fluids for certain categories of patients would not obviate the need for ambulances to carry fluids nor personnel to be trained with the skills required to administer them; on-scene times represent a small proportion of total time so that changes in these would have no cost consequences for the service.

A more detailed cost-effectiveness analysis was not undertaken because there is insufficient reliable information available about the relative consequences of different strategies, particularly with respect to blunt trauma (the predominant type trauma in UK) and long term morbidity and mortality. Given the similarity in costs between different policies, what is needed to populate a decision analytic model is better empirical evidence about the relative consequences in terms of morbidity, mortality and hospital utilisation of different strategies.

Need for further research
Further research would be needed to establish whether hypotensive (i.e. cautious) resuscitation is more effective than delayed or no fluid replacement, and whether IV fluid resuscitation in blunt trauma should be more aggressive than in penetrating injury, as implied by current guidelines.

New fluids should not be adopted for use without being shown to be superior to alternative treatments in high quality clinical trials, which, in the light of the current lack of evidence for the benefits of fluids, should include an arm with a very cautious fluid resuscitation protocol.

Routinely collected data for ambulance call-outs should be analysed and reported and the quality of data collection and analysis improved.

Conclusion

We found no evidence to suggest that pre-hospital IV fluid resuscitation is beneficial. There is some evidence that it may be harmful and that that patients do comparatively well when fluids are withheld. However, this evidence is not conclusive (particularly for blunt trauma) and is not sufficient to contradict the Consensus Statement and JRCALC guidelines which recommend hypotensive resuscitation.

As the Consensus Statement, and to a lesser extent the JRCALC guidelines, represent a more cautious approach to fluid management than previously advocated, the implementation of these should be supported.

ABBREVIATIONS

A&E	Accident & Emergency
AIS	Abbreviated Injury Scale
ALS	Advanced Life Support
ATLS	Advanced Trauma Life Support
BLS	Basic Life Support
BNF	British National Formulary
BP	blood pressure
EMT	emergency medical technician
GCS	Glasgow Coma Score
HS	hypertonic saline (7.5%)
HSD	hypertonic saline (7.5%) with 6% dextran 70
HTA	health technology assessment
ICU	intensive care unit
ISS	Injury Severity Score
ITT	intention to treat
IV	intravenous
NEAS	North East Ambulance Service
PPF	plasma protein fraction
RCT	randomised controlled trial
RTA	road traffic accident
RTS	Revised Trauma Score
PRF	patient report form
SAST	Sussex Ambulance Service Trust
SBP	systolic blood pressure
TARN	Trauma Audit Research Network
TKVO	to keep vein open
TRISS	Trauma Score-Injury Severity Score
WMAS	West Midlands Ambulance Service

1. AIM OF THE REVIEW

This report systematically reviews the evidence about the effectiveness and cost-effectiveness of the pre-hospital administration of intravenous (IV) fluids in trauma patients who have haemorrhage-induced hypotension due to trauma and no head injury.

The main focus of the report is the overall question of whether IV fluid replacement (versus no IV fluid replacement) should be undertaken in the pre-hospital setting. However, to help answer this question the report also considers the evidence about the effect of early versus delayed pre-hospital fluid administration and the volume of fluid infused. There are three main ways in which IV fluids resuscitation may influence the outcome for trauma patients:

- effects on circulating volume and blood pressure
- physiological effects of the fluid other than as a fluid replacement
- delay of definitive treatment

There are many issues surrounding pre-hospital fluid administration, including the choice of fluid, type of infusion (e.g. rapid or controlled), type of trauma (e.g. blunt or penetrating) and trauma in children. Whilst it is not possible to undertake *de novo* systematic reviews for all these subsidiary questions within the scope of this assessment report, we consider the evidence underlying these issues and the implications for the use of pre-hospital fluids using existing systematic reviews where available.

2. BACKGROUND

2.1 Description of underlying health problem

2.1.1 Haemorrhagic shock

One of the major causes of death in trauma patients is from the consequences of hypovolaemic shock due to bleeding.

"Shock" is a term used to denote circulatory failure leading to inadequate perfusion and oxygenation of the tissues. Shock can cause permanent damage to essential organs and may lead to multiple organ failure and death.

Shock can have a number of different causes. These can be broadly classified as

- Hypovolaemic (e.g. from bleeding)
- Vasogenic (e.g. from changed permeability or tone of blood vessels in anaphylactic shock, septicaemic shock or neurogenic shock)
- Cardiogenic (e.g. from pump failure due to myocardial infarction or rhythm disturbance, cardiac tamponade or tension pneumothorax)

Shock is usually classified into four degrees of severity as shown in Table 1, below.

Table 1 Classification of shock*

	Class I	Class II	Class III	Class IV
Blood loss *(based on a 70kg male)*	<750ml	750-1500ml	1500-2000ml	>2000ml
% Blood loss	<15%	15-30%	30-40%	>40%
Pulse rate/minute	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal or Increased	Decreased	Decreased	Decreased
Respiratory rate /minute	14-20	20-30	30-40	>35
Mental state	Alert	Anxious	Confused	Lethargic
Urine output ml/hr	>30	30-20	20-10	10-0
Extremities	Normal	Pale	Pale/cool	Pale/clammy

* Adapted from Greaves and Porter 1999[1]

It should be noted that this classification, which is widely accepted, is based on clinical observation and animal models only and, for ethical reasons, has not been validated in any clinical study (Porter and Bickell, personal communications).

As can be seen from Table 1, until blood loss is over 30% of blood volume the clinical signs of shock can be minimal and can pass unnoticed. However, it is also the case that systemic arterial hypotension after acute blood loss does not necessarily represent a state of actual or impending shock. This has been observed in the military arena,[2] animal studies (where hypotension could be sustained for several hours without inducing shock)[3] and in clinical trials where a substantial proportion of hypotensive patients with trauma had no evidence of hypoperfusion, such as base deficit or impaired urine output (Bickell, personal communication). In otherwise fit individuals significant blood loss may occur without evidence of abnormal tissue function.

The fact that the neither relationship between blood loss and blood pressure, nor that between blood pressure and shock are linear makes diagnosis of shock or impending shock difficult in the field. It is imperative therefore that a simple measure is used to determine the presence of shock, customarily the presence or absence of a radial pulse in adults. At the present time there are no field tools that provide a prompt diagnosis of shock based on deranged biochemistry.

2.1.2 Homeostatic mechanisms in response to blood loss

The body responds to bleeding in a variety of complex and interacting ways that tend to act to reduce blood loss and preserve vital organ perfusion. Relatively immediate compensatory mechanisms include the following:

1. Activation of the clotting cascade to reduce blood loss.
2. Autonomic responses lead to an increase in vascular tone and the release of adrenaline and noradrenaline, which have a positive inotropic effect on the heart and increase the heart rate. Autonomic responses help maintain blood pressure by increasing the systemic vascular resistance and reducing the capacity of the venous circulation thereby increasing cardiac return.

3. Blood flow may be diverted from the peripheries to maintain vital organ perfusion.
4. Hormones such as steroids, glucagon, aldosterone and antidiuretic hormone are also released by the body and act to sustain the circulating volume.
5. Decreased renal perfusion stimulates renin release, which in turn increases angiotensin II, a potent vasoconstrictor.

2.1.3 Traditional approaches to minimise shock

Because shock is associated with organ damage and death, interventions to minimise or reverse it has been one of the major objectives of emergency or pre-hospital care. Traditionally the management of trauma patients suffering from haemorrhagic shock has included early, rapid intravenous fluid replacement on the grounds that increasing the circulating volume and blood pressure will help maintain vital organ perfusion thereby improving outcomes and survival.[4]

In the 1970s and 1980s, in order to ensure the earliest possible replacement of fluid, paramedics were increasingly trained in cannulation and fluid resuscitation so that injured patients could be treated on scene before their transfer to hospital. The position is expressed in the following quote from the early 80s.

> *"There is a growing body of thought that claims that it is important to initiate resuscitation as soon as possible and to perform a limited number of definitive interventions to stabilize a trauma patient before transportation to a trauma care facility."*[5]

As pre-hospital fluid resuscitation of patients by paramedics trained in Advanced Life Support (ALS) grew during the 1980s so did the debate about the relative benefits of ALS compared to basic life support (BLS). Opponents of ALS argued that BLS was more appropriate as it minimised on-scene delay and therefore the time to definitive operative treatment (thought to be the single most important factor for influencing survival from injury). The two positions in this debate were characterised as "stay and play" or “treat in the street” versus "scoop and run" or “load and go” ("scoop and run” refers to: open the airway, ensure ventilation, arrest external haemorrhage and load and go).

As observational data began to accrue that suggested that ALS was not necessarily associated with improved survival and could cause delay in the time to arrival at hospital the "scoop and run" strategy began to gain increasing support. Guidelines for pre-hospital treatment of trauma patients increasingly emphasised that fluid replacement should not be at the expense of delaying time to definitive hospital treatment (for example the Consensus Statement published by Greaves *et al* (2002) in the Journal of the Royal College of Surgeons of Edinburgh which state "Transfer should not be delayed by attempts to obtain intravenous access".[6]

2.1.4 The pathophysiological arguments behind treatment strategies

Although "scoop and run" is now widely supported in the UK for trauma victims, to avoid the net harm from delay to definitive treatment, there is still lack of consensus about whether fluid resuscitation *per se* is beneficial or harmful.[7,8]

Discussions with clinicians and paramedics during the preparation of this report revealed a wide variation in opinions in the clinical and paramedical community, and that many people have very strong beliefs despite the wide variation in opinions and lack of direct evidence about the effect on mortality of the strategy they advocate.

Much of people's beliefs about the utility of fluid resuscitation is based on pathophysiological reasoning. Thus those who support fluid replacement do so on the grounds that since shock and the degree of shock is directly related to risk of death it must be reversed by replacing circulating volume and maintaining blood pressure. This was supported by the early experimental models in which animals were bled by a specific amount or to a specific blood pressure. In these experiments, those animals that were resuscitated with fluids tended to have better survival.[3]

The belief in the need to maintain circulating blood volume and blood pressure was so strong that many of the subsequent observational and experimental studies undertaken or cited in support of fluid replacement simply use these surrogate endpoints as their outcomes and assumed that since these are correlated with survival in the trauma patient, restoring their values towards normal via fluid replacement will be correlated with improved survival.

The use of surrogate endpoints on the basis that they are correlated with natural history can be misleading - after all we would not slow a tachycardia in a shocked patient because the heart rate goes up with blood loss and is correlated with poorer prognosis! Moreover, in the 1980s people increasingly began to question whether fluid replacement might actually be harmful and increase blood loss through the dilution of clotting factors and mechanical disruption of blood clots from increased blood pressure, thereby exacerbating the shock. The relevance of the early animal studies, which modelled a situation where bleeding had stopped, to the trauma situation, where haemorrhage is often uncontrolled, was questioned. Later animal studies attempted to model uncontrolled haemorrhage to better mimic the clinical situation. These were suggestive that fluid resuscitation might indeed be harmful.[9,10]

The complexity and interactions of the homeostatic mechanisms mean that it is not possible to predict reliably from first principles the consequences of interventions. Thus, although hypotension is associated with adverse outcomes for shock, it may actually be protective by, not only preventing clots being disrupted, but also by serving as a trigger for the recruitment of vital responses (such as renin release) or by influencing the physiological redistribution of blood flow from the peripheries to the vital organs. It is not necessarily the case that because lower BP is associated with a worse prognosis restoring BP will improve the prognosis. Thus studies that use only surrogate endpoints (such as blood pressure and heart rate or composite measures of these such as the Trauma Score) should be interpreted with caution as effects on mortality are not predictable.

However, not only is it difficult to predict the pathophysiological consequences from first principles there is the added complexity of the balance between competing benefits and harms. For example even if IV fluid resuscitation does increase the immediate risk of death from haemorrhage it could still be reducing the risk of later death or morbidity from multiple organ failure and the balance of these risk and benefits needs to be clearly established.

It is also important to realise that not all fluids have the same characteristics (see 2.3.3, below for details of fluid types) and that the choice of fluid can have important direct pharmacological and other effects including: ability to expand and sustain circulating volume, distribution across the intravascular and extravascular compartments, the risk of fluid overload, hypernatraemia, acidosis, direct interference with the coagulation cascade, interstitial oedema and the risk of adult respiratory distress syndrome, septic complications, effects on vascular or gut permeability, direct inotropic effects, direct effects on vasoregulation, effects across the blood-brain barrier, immunological and inflammatory effects (e.g. on T-cell, macrophage and neutrophil regulation and function). In assessing the benefit and harm of IV fluids, therefore, it cannot just be assumed that all fluids will have the same direction of effect and combine them together in a meta-analysis.

2.2 Epidemiology

Burden of disease

Trauma is an important cause of death and disability worldwide - road traffic accidents were ranked as the 9th and violence as the 16th most common causes of death in 1990.[11] It is the commonest cause of loss of life in those under the age of 40 and the burden of trauma is set to increase in the next 20 years. Moreover trauma is becoming increasingly important as a cause of death worldwide with modelling suggesting that deaths from injury will increase from 5.1 million in 1990 to 8.4 million in 2020,[11] becoming the second highest cause of 'life years lost' through premature death or disability.[12]

Data from the Office of National Statistics (ONS) states that in England and Wales there were 16,526 deaths from injury and poisoning in 2000, with 63% of incidents in men and 37% in women.[13] Deaths from injury accounted for 15,462, with 3,032 cases due to transport accidents (20%), 4,281 due to falls (28%) and 3,480 due to suicide or self-injury (23%). More than half of all deaths in females occurred at age 75 or over, whilst less than one fifth of deaths in males were at these ages. Department of Transport data from 1998 states that there were approximately 320,000 injuries involving road vehicles and around 3,400 deaths. 71% of drivers and riders involved in injury accidents were male, and 24% of drivers and riders involved in accidents were aged between 16 and 24.[14] Data from the Royal College of Surgeons from 1988 estimated that there were 545,000 annual trauma admissions in the UK in 1988 and around 14,500 annual fatalities. There is currently no national injury reporting system. Hospitals can submit data to the Trauma Audit and Research Network (TARN), however contribution is not mandatory. Around 110 hospital currently submit data (personal communication Dr Omar Bouamra, TARN).

Deaths due to trauma

The TARN database shows that most deaths due to trauma involve patients with head injuries. (TARN, personal communication) We also looked at routinely collected data from the West Midlands to address this question.

In England, all acute in-patient activity is subject to a Minimum Data Set (MDS) captured routinely and downloaded to a central source, Hospital Episode Statistics (HES). HES uses ICD version 10 codes to describe disease, injury and adverse effects of external causes. There are a total of seven diagnosis fields for each episode of care.

Although hypovolaemic shock does have a specific ICD10 code (R57.1) it resides in a section of the coding system whose codes (anecdotal evidence suggests) are not applied as

rigorously as those parts of the system that describe specific traumas or pathologies. This was corroborated by an analysis of all admissions to West Midlands hospitals in financial year 2000/2001 (approximately 10% of the English total), where the code was only used in 17 admissions. Hence target subjects do not leave a distinct 'footprint' in routinely collected data in English hospitals. However HES can identify admitted cases with trauma likely be associated with significant bleeding.

A further search was run on admissions for the West Midlands for one calendar year, 2000-2001. Injuries are largely categorised according to a crude structure. The area of body first, followed by sections describing the type of injury, typically: superficial, open wound, crushing, fractures, dislocations, injury of blood vessels, injury of muscle and tendon, injury of nerves, multiples. A selection strategy was used which focussed upon the first three diagnostic fields of the MDS which would contain main primary diagnosis and significant others. All emergency injury admissions were selected and the following cases were excluded: episodes with just joint, nerve, muscle or tendon injuries and where all injuries were classed as "superficial". Episodes involving fractures alone were also excluded, although many fracture patients who had sustained other target injuries would have been included. Injuries to hands or fe*et al*one were disregarded (except for traumatic amputation). Traumatic injury of all the thoracic, intra-abdominal and pelvic organs were included.

All cases of head injury were excluded, unless the injury was described as "superficial" and the patient had also presented with other injuries in the inclusion criteria.

This gave a total of 2394 admissions. Of these 2212 (92.4%) were discharged to usual or temporary residence (i.e. not a health or nursing care provider). 876 (36.6%) were discharged in this manner in less than 48 hours of admission. Only 34 (1.4%) of these patients died in hospital. (The exclusion of head traumas affects the number of episodes greatly. In the same period there were 5416 admissions where at least one of the first three head diagnostic fields contained head injuries. These included facial injuries but excluded episodes where only eye injuries were sustained or all injuries recorded were classed as superficial. In this cohort a total of 67 individuals died in hospital following admission. (Gavin Rudge, personal communication)

The small percentage of trauma patients who died in hospital suggests that there are very few non-immediate deaths due to hypovolaemic shock alone (i.e. not associated with head injury). There is thus limited potential health gain from improving pre-hospital trauma care unless it can prevent deaths before arrival at hospital. Even then, most people who die before hospital admission are dead before the ambulance crew can attend them (see **timing of trauma deaths**, below).

Type of trauma

The majority of trauma seen in the UK is blunt trauma. A commonly cited proportion is a ratio of 1:10 penetrating injury to blunt injuries. Of 91,602 records in the Trauma Audit Research Network (TARN) database collected from 97 hospitals in England, Wales and Ireland between 1989 and the end of 1997, 97.5% related to blunt injuries, and 2.7% related to penetrating injuries.[15] This suggests a ratio more like 1:36. This is broadly consistent with the Nicholl HTA report[16] which reported a range of 2.3%-7% (mean 4.8%) of penetrating injuries in a selected sample of seriously injured trauma patients.[16] This contrasts with the United States where civil violence is a major cause of trauma and the blunt to penetrating

injury ratio is approximately 1:1.[1] The commonest causes of blunt injuries were road traffic accidents (36.3%), falls less than 2 metres (33.1%), falls over 2 metres (13.4%) and assaults (5.4%).

Timing of trauma deaths

A survey of trauma deaths in the South West Thames Region found that 58% of the 434 recorded trauma deaths occurred prior to arrival at hospital.[17] A Scottish study investigated the time of death after trauma.[18] Over two years, there were 331 trauma deaths (Lothian and Borders Regions) in patients aged over 12. Of these, 253 (76.4%) died within one hour (74.9% were found dead, died instantaneously or had unsurvivable injuries; 1.5% died in transit to hospital), 78 patients (23.6%) survived for more than one hour and 59 (17.8%) survived for more than four hours. A similar study conducted over an 11 year period for children aged less than 15 years found that there were 138 trauma deaths, of which 99 (71.7%) occurred within 1 hour after the injury, 5 (3.6%) within one to four hours and 34 (24.6%) after four hours.[19] A North Staffordshire based study found 497 deaths from accidental injury in a three-year period (1987-1990, population 500,000). After excluding deaths by suicide, by hanging and deaths after fracture of the neck of the femur (not a direct consequence of the fracture), 409 deaths remained. 152 of deaths (37%) occurred pre-hospital and all occurred before paramedical or medical help arrived. Around half were due to road traffic accidents.[20]

2.3 Current service provision

Personnel

Ambulance services across the UK have differing mixes of personnel. Ambulance crew can either be emergency medical technicians (trained in BLS) or paramedics trained in advanced life support (ALS) techniques such as endotracheal intubation, cannulation and administration of drugs and IV fluids. Ambulances usually have one driver and one attendant and can be manned by technician-only, paramedic-only or mixed crews. It is Department of Health policy that all emergency calls are attended by an ambulance including a trained paramedic but this is not always what happens in practice.[21] A 1998 health technology assessment (HTA) of paramedic skills in pre-hospital trauma care looked at three ambulance services in England.[16] The ratio of emergency medical technician-only crews to crews with at least one paramedic varied across the services. In one area there were very few technician-only crews. In the second area full follow up showed approximately one technician-only crew for every 6-7 crews (13%) with a paramedic. In the third area, in which crews were randomly sampled, the ratio was approximately 2:5 (technician-only : paramedic crews), or 29% technician-only crews. Verbal enquiries by us to ambulance services suggest that in 2003 nearly all crews will have at least one paramedic and only in exceptional circumstances (e.g. when there a staff shortages due to illness) would an ambulance have a technician-only crew.

There is additionally a voluntary service by doctors, BASICS, who are trained and equipped to attend accidents.

Patient management policies

The current official recommendations for fluid resuscitation in the ambulance service are the JRCALC guidelines that were produced in 2002 and are in the process of implementation.[22] The main fluid for trauma resuscitation is Hartmann's solution, a crystalloid, and physiological saline for other indications such as dehydration or diabetic ketoacidosis,

although saline may also used in hypovolaemic shock. Haemaccel and other colloids are being phased out as the new JRCALC guidelines are implemented (Ham Patel, Personal Communication.) There is also a Consensus Statement giving guidelines for the treatment of trauma produced be a number of organisations.[6] Both these sets of guidelines have recently been modified and details are given below (the full Consensus Statement and extracts from the JRCALC guidelines are given in Appendix 1 and Appendix 2 respectively).

2.3.1 Consensus Statement [6]

In 2000 a number of organisations in the UK came together to produce a Consensus Statement on pre-hospital trauma care based on the best currently available evidence supplemented by consensus based on clinical experience where evidence was equivocal, weak or not available. The organisations involved were the Royal College of Surgeons of Edinburgh (Faculty of Pre-hospital Care & Faculty of Accident & Emergency Medicine), The United Kingdom Military Defence Forces, Ambulance Service Association (ASA) with paramedics representatives, British Association for Immediate Care (BASICS), London Helicopter Emergency Medical Service (HEMS) and researchers with an interest in pre-hospital care. Their conclusions were for a cautious fluid resuscitation policy rather than aggressive fluid resuscitation. In particular they recommend:

- *Transfer should not be delayed by attempt to obtain intravenous access*
- *Cannulation should take place en route where possible*
- *Only two attempts at cannulation should be made*
- *Entrapped patients require cannulation at the scene*
- *Normal saline is recommended as a suitable fluid for administration to trauma patients*
- *Boluses of 250ml fluid may be titrated against the presence or absence of a radial pulse (caveats; penetrating torso injury, head injury, infants)*

2.3.2 Joint Royal Colleges Ambulance Liaison Committee (JRCALC) guidelines

The JRCALC guidelines[22] formally adopted the Consensus Statement guidelines. There were some subsequent adjustments, notably the recommendation that 500ml of saline should be given, whereas the Consensus Statement recommends aliquots of 250ml. The JRCALC guidelines state that:

> *'...current research shows little evidence to support the routine use of pre-hospital IV infusion in trauma patients. In cases of penetrating chest and abdominal injuries and aortic aneurysm dissection, an actual decrease in survival has been associated with pre-hospital fluid administration, by displacing fragile blood clots from bleeding vessels and causing re-bleeding. As a rule, IV infusions should be commenced en route to hospital, and only sufficient fluid given to maintain a systolic BP of 80-90 mmHg. 500 ml IV of crystalloid solution should be given, and the effects on the circulatory system assessed, before further fluids are given.'*

The crystalloids recommended by the JRCALC guidelines are compound sodium lactate (Hartmann's Solution or Ringer's Lactate) and 0.9% saline. It does not recommend hypertonic saline solutions and large molecule starch compounds as these are currently being evaluated. It discourages use of colloids in pre-hospital care *"as they have no proven benefit but a higher cost and higher risk of adverse reaction."*

2.3.3 IV fluid use in practice

We searched the literature to identify evidence about ambulance and paramedic activity to assess the degree to which practice corresponds to current guidelines.

Enquiries with the Ambulance Services Association (ASA) identified that there are routinely collected data in the form of data sheets that are completed for each call out, however these data are not co-ordinated nationally nor reported routinely at a local level (see Appendix 7 for agreed minimum data set). So despite ambulance crews having to fill in comprehensive patient report forms (PRFs) that record dozens of fields about a patient's condition, aetiology of injury, demographic characteristics and treatment we found little published data about actual practice. We were told by audit departments that although the data is input into computers there were no routine analyses that could inform this question. In one area (Shropshire) where PRFs were said to be routinely analysed we were unable to obtain an up-to-date report.

Some partial audit information was found and is reported below. However, there are also problems with reliability of the data and accuracy of recording that limits the interpretation of the findings. When we enquired with trauma.org about the proportion of trauma patients who received fluids in the UK we were told that

> *"All patients would be CONSIDERED for fluids. (Perhaps not all should receive but currently in the UK almost all will)…[the] approximate percentage of trauma patients who receive fluids [is] currently 100%"* (email communication 17/05/03)

North East Ambulance Service Audit: (NICE submission from JRCALC)
Of 62,145 patient report forms studied over a period of 3 months, 192 record IV fluid administration of which 43 were identified as trauma. The breakdown of the latter was said to be 17 RTAs, 5 falls, 1 burn and 3 assaults. This raises questions about the quality of recording as the categories only account for 26 of the 43 cases identified as trauma. No information is reported on the reason for administration of IV fluids in the 149 other patients. It is possible that some of these were also non-burns trauma patients in whom this data was either not recorded or reported. Only 2 patients were recorded as requiring more than 1 litre of saline. There was no linkage of the data on the requirement for IV fluids and outcome (e.g. mortality rates).

The area covered by the service serves a population of approximately 2 million, which results in an estimated 8.6 patients per year given fluids for trauma per 100,000 population. If burns are excluded, this figure may be slightly smaller. If there is misclassification and the 149 patients who received fluids where the indication is not reported actually received it for hypovolaemia due to blood loss the rate could be as high as 38 per 100,000 population. In addition, the data only indicates whether an intravenous infusion was set up, actual volumes administered are not recorded. Intravenous fluid therapy subsequently used in the A&E department is not recorded, nor is there any mechanism for assessing whether the use of IV fluids in a particular case is deemed medically appropriate.

Welsh Ambulance Service Trauma Audit: (personal communication Karen Pitt)

Analysis of 5 months of data showed that 308 trauma patients (excluding burns, smoke inhalation, drowning and asphyxia) received IV fluids. The area covers a population of approximately 2.9 million, which results in an estimated 25.5 patients per year per population of 100,000 receiving fluids. Again, this does not give information on appropriateness of use or volumes infused (either pre-hospital or in the A&E department).

Sussex Ambulance Service Trust: (personal communication Angela Fitzpatrick and David Janes)
An audit was conducted by the Sussex Ambulance Service Trust (SAST). All trauma patients (n=1730) from a randomly selected month (October 2002) were included in the analysis. The criteria for being included in the audit were: fractures, falls, haemorrhages, hypovolaemic shock, road traffic or train collisions, head injuries, spinal injuries, wounds or lacerations or traumatic injuries from animal or human bites, shootings, stabbings, hanging or rape. Patients with burns, drowning, heat stroke, hypothermia, electric shock and smoke inhalation were excluded.

Eighty-one patients (5%) were given IV fluids (Hartmann's solution, 500 ml bags). A total of 108 bags were given to 81 patients, an average of 1.3 bags per patient. The timing of fluid administration was recorded in 54 patients (67%): despite the Consensus Statement advising that fluids should be given en route where possible, 45 (83%) of patients were given fluids at the scene, whilst 9 (17%) were given fluids en route to hospital. Crews averaged 17.7 minutes (2-51 minutes) from arrival on scene to first IV fluid administration. Based on a population of approximately 1.5 million, around 65 patients per 100,000 population per year receive fluids.

The estimates thus range between 8.6 and 65 per 100,000 population who receive pre-hospital fluids for trauma. Thus in England & Wales, with a population of approximately 57 million, there may be somewhere between 5,000 and 37,000 people who receive pre-hospital IV fluids for trauma. These figures may well be underestimates because of poor recording, or may be overestimates as crews tend to record when bags were put up but not whether they were still full on arrival at the hospital which is not unusual (personal communication).

TARN database (personal communication Dr Omar Bouamra)
Records from the TARN database show that between 1988/89 and 2003, 180710 trauma cases were registered (including burns). This is based on the contribution of data from 110 hospitals, so does not give an overall estimate of trauma cases for the whole country. Of these patients 10.8% had a peripheral line at the scene, 18.3% had no line and for 70.9% of patients this information was not recorded. An average of 323 ml of fluids were given (range 144-1052 ml, with increasing amounts being given for higher Injury Severity Scores). Again this is based only on those cases where information was recorded. The recording of fluid administration in A&E is more comprehensive, with information only missing in around 27% of cases.

Frequency of seeing a patient with hypovolaemic shock
The ability of personnel to deal with clinical conditions will depend on their familiarity with the situation. The Shropshire Ambulance Service reported that a crew would expect to see a patient with hypovolaemic shock approximately 2-4 times a year (Mr Ham Patel, personal

communication). Rates will vary depending on whether it is a rural or urban setting, or near major roads etc.

2.4 Description of the intervention under consideration

2.4.1 Type of patient

IV fluids are used to treat shock resultant from a number of different aetiologies. This review is limited to considering patients with haemorrhage-induced hypotension resulting from trauma. However trauma can produce different types of injury. All types of injury are considered here (penetrating, blunt, thoracic, abdominal, peripheral etc) with the exception of patients with isolated or concomitant head injuries. The pre-hospital treatment of patients with isolated or concomitant head injuries was excluded from the scope of this review requested by the National Institute for Clinical Excellence (NICE) as the issues concerning the avoidance of secondary cerebral damage from hypoperfusion in the head-injured patient[1] and keeping intracranial pressure from rising too high would have added to the complexity of the report and there is a greater consensus within the clinical community about fluid resuscitation in head injury.

2.4.2 Criteria for treatment

Different guidelines suggest different thresholds for initiating IV fluids in the trauma patient. Shock is normally classified into 4 different levels of severity. Different protocols for resuscitation include different thresholds for initiating fluids. Current guidelines suggest titration until a peripheral pulse is felt except for penetrating injuries when a carotid pulse is sufficient.[6] We will be exploring the evidence base to determine if there is evidence for particular thresholds where IV fluid resuscitation is likely to be particularly beneficial, harmful or unlikely to alter outcome greatly.

2.4.3 Types of fluids

There can be a wide range of fluids that have been used in, or are proposed for, pre-hospital resuscitation of the hypovolaemic patient. These can be broadly classified into crystalloids, colloids, crystalloid/colloid mixes, blood and the newer blood substitutes (products capable of carrying oxygen to the tissues). The most widely used and advocated fluids are the crystalloids and to a lesser extent the colloids.

Crystalloids

Crystalloids are salts that are dissolved in water. There are several commonly used crystalloids (e.g. Ringer's lactate, saline, Hartmann's solution, dextrose, dextrose/saline). Since the electrolytes composing these solutions can pass through the cell membrane, crystalloids will distribute throughout the intravascular compartment. Crystalloids can be isotonic, hypertonic or hypotonic. The term "isotonic" means that the osmotic pressure exerted by the fluid is the same as physiological levels and thus there would not be expected to be a net movement of water across cell membranes. Given that solutes can cross the membranes only approximately 25% of the infused isotonic fluids will be expected to stay in the intravascular compartment as the fluid will distribute across the intra and extravascular spaces. This means that 2 to 4 times the amount of blood lost must be infused to maintain the same circulating volume. One of the suggestions to explain the failure of some studies to demonstrate improved outcomes with fluid resuscitation has been the idea that isotonic solutions can increase the risk of volume overload and pulmonary oedema when infusing large volumes of crystalloids. Hypertonic solutions have been proposed as superior since

they would be expected to draw in water from the surrounding cells. This not only would require lower volumes to produce the same expansion in circulating volume as isotonic solutions, it has been suggested that hypertonic solutions could be used to expand the intravascular volume by more than the transfused volume as fluid would be transferred from the extravascular compartment and cells.

Colloids
Colloids are suspensions of molecules of different sizes. Colloids can be made from starch (e.g. hetastarch), gelatin (e.g. Haemaccel), polysaccharides (e.g. dextrans) or proteins (e.g. albumin). Colloids are considered by some to be more "efficient" than isotonic crystalloids in fluid replacement as the larger molecules have restricted passage through the cell membrane so that a large percentage of the administered volume remains in the intravascular compartment. They can also exert oncotic pressure. Colloids are currently being withdrawn from ambulance equipment as the new JRCALC guidelines are implemented (Ham Patel, personal communication.

Blood and blood substitutes
Blood and blood substitutes are not considered in this review. Blood is not generally available in the pre-hospital setting and oxygen-carrying blood substitutes are still experimental.

The purpose of this report is to consider the general question about the effectiveness of pre-hospital fluid resuscitation but this is difficult to separate out from the question about the effectiveness of a particular solution used. In the timescale given it would not be possible to undertake a systematic review of the comparative effectiveness of all the different fluids with each other. Therefore we have undertaken a systematic review of the primary research evidence addressing the former question and have sought high quality secondary research evidence from systematic reviews to inform the second question.

2.4.4 Personnel involved

Cannulation and initiation of IV fluids can be undertaken by doctors or by trained paramedics but not emergency medical technicians.

2.4.5 Setting

The question under consideration in this review is the pre-hospital administration of fluids. However, where research evidence is not available from a pre-hospital setting to address a particular issue, we examine what evidence there is from other settings that may inform the question.

2.4.6 Equipment required

Cannula, IV giving sets and IV fluids are required to administer IV fluids.

2.4.7 Follow-up required

The major outcome of interest from the administration of IV fluids is survival. Most patients who die from trauma do so in the first few days. Death from complications of shock would normally occur within 28 days. However, TARN data shows that 6% of deaths occur in the period between four weeks and three months.[23] Furthermore the report by HTA by Nicholl *et*

al[16] suggests that there were morbidity consequences of the method of pre-hospital treatment at six months post injury.

2.4.8 Degree of diffusion

IV fluid resuscitation is highly diffused into clinical practice. In the UK the commonest fluids used are crystalloids. Hypertonic solutions are not widely used.

2.4.9 Anticipated costs

Fluid costs
Fluid costs and costs of other equipment are given in Table 2 and Table 3 below, respectively.

Table 2 Costs of fluids

	Unit size	Price	Source
Saline 0.9%	500 ml 1 litre	£ 0.38 £ 0.65	WMAS, personal communication Chris Upton NEAS, personal communication Tom Clarke
Hartmann's solution	500 ml	£0.51	SAST, personal communication Angela Kirkpatrick
Haemaccel®	500 ml	£3.71	BNF[24]
Gelofusine®	1 litre	£9.45	
Dextran 70	500ml	£4.78	
Dextran 40	500ml	£4.56	
Hetastarch	500ml	£15.57	
Hexastarch	500ml	£12.50	
Pentastarch	500ml	£11.25	
HyperHAES®	250ml	£28.00	Submission to NICE from Fresenius Kabi Limited

Table 3 Cost of a cannula and giving set

	Price	Source
IV set (cannula, giving set)	£1.23 £1.31 £1.32	NEAS, personal communication Tom Clarke WMAS, personal communication Chris Upton SAST, personal communication Angela Kirkpatrick
Cannula and saline flush Cannula (sharp safe) and saline flush	£1.11 £2.36	WMAS, personal communication Chris Upton SAST, personal communication Angela Kirkpatrick

Personnel costs
In Shropshire Ambulance Service the salary of an emergency medical technician is currently £18,079. There are no increments for experience or length of service. The salary for a paramedic is the same with enhancements for skills giving a total salary of £19,287. Again there are no increments for experience. (Ham Patel, personal communication)

The 2001 unit cost of crew wages per successfully completed ambulance journey, allowing for the costs of "abortive" journeys is £99 for a paramedic crew and £96 for a emergency ambulance crew.[25]

Paramedics have eight additional weeks training compared to technicians. However the impact of the cost of this is negligible within the total costs and the Unit Cost of a paramedic unit, an emergency ambulance and patient transport service for overheads and management, including training is identical for the three services (£105).[25]

3. EFFECTIVENESS

3.1 Methods for reviewing effectiveness

3.1.1 Search strategy

The primary question addressed by this review is how effective IV fluids are in the resuscitation of hypovolaemic trauma patients with no head injury in a pre-hospital setting. Preliminary scoping searches suggested that high quality randomised controlled trial evidence directly addressing this question was unlikely to be sufficient to provide an unequivocal answer to this question. We therefore decided to look at evidence from other settings that may be generalisable to the pre-hospital setting.

Two separate search strategies were used: a highly sensitive search strategy, designed not to miss any relevant studies, was developed to identify studies relating to the use of fluids in a pre-hospital setting (immediate versus delayed fluids, different volumes, or speed of infusion), and a more specific search strategy was used to identify additional RCTs of fluid administration in other settings (e.g. after admission to hospital), as tens of thousands of studies would have otherwise been identified. Full search strategies are listed in Appendix 3.

Databases:
The following electronic databases were searched: the Cochrane Central Register of Controlled Trials (Issue 1, 2003), MEDLINE (OVID, 1966-2003), EMBASE (OVID, 1980-2003) and the Science Citation Index (1980-2003).

Strategy:
Text and MeSH terms relating to the population (e.g. trauma, hypovolaemia), the intervention (e.g. IV fluid, fluid resuscitation) and the setting where applicable (e.g. pre-hospital, emergency) were combined with filters for randomised controlled trials. There were no language restrictions.

Citation searching, handsearching:
In addition, citation lists of relevant publications (included studies and reviews) were checked and the Journal of Trauma, Injury, Infection & Critical Care was hand searched for the years 1998 (volume 44) – 2003 (volume 54 (2)) inclusive.

Unpublished data:
Unpublished data were sought by contacting organisations and individual experts, and by checking research registers of ongoing trials and other relevant web sites (list of web sites searched in Appendix 1). Data from the industry and other submissions were checked for relevant published and unpublished studies.

Additional questions
A - What is the effect of basic life support (BLS) versus advanced life support (ALS) on patient outcome?

B - What is the effect of fluid replacement for different types of injuries (e.g. blunt, penetrating) on patient outcome?

C - What is the effect of different types of fluid (e.g. different crystalloids or colloids or crystalloids versus colloids) on patient outcome?

D - What is the effect of fluid replacement in paediatric trauma patients?

E - How accurate are paramedics at diagnosing hypovolaemia in trauma patients at the scene and can this affect patient outcomes?

F - Is there evidence on whether naturally occurring physiological shock mechanisms have a protective effect? How does fluid resuscitation interact with these mechanisms?

In order to identify the evidence base concerning additional relevant issues relating to fluid replacement, search strategies were developed to identify systematic reviews relating to these issues. Search filters for reviews were combined with relevant MeSH terms and text words. The following databases were searched: Cochrane Library (Issue 4, 2002), MEDLINE (OVID, 1966-2003) and EMBASE (OVID, 1980-2003). There were no language restrictions. Individual randomised controlled trials were not systematically sought.

Observational studies
A separate systematic review of observational studies was ruled out at the protocol stage as these would not have informed the question adequately due to the intrinsically confounded nature of the study designs. However, some observational studies are frequently cited. Therefore, for the purpose of providing an adequate appraisal of current policy, all observational studies cited in the Consensus Statement or JRCALC guidelines were retrieved and critically appraised.

3.1.2 Inclusion and exclusion criteria

Primary research question: Immediate versus delayed fluid replacement or differential volume replacement in a pre-hospital or other setting

Inclusion criteria:

Study design	Randomised controlled trials
Population	Patients of any age with haemorrhagic hypovolaemia resulting from trauma
Intervention	Immediate or early fluid replacement (pre-hospital or other setting)
Comparator	Delayed or no fluid replacement (pre-hospital or other setting) Different volume of fluid given (pre-hospital or other setting) Fluids given at different speed (pre-hospital or other setting)

Exclusion criteria:

Study design	Observational studies
Population	Randomised controlled trials* with primarily: • Head injured patients • Patients with burns • Patients with septic shock
Intervention/ Comparator	Randomised controlled trials comparing different types of fluids Randomised controlled trials comparing blood or blood products to other fluids

* Studies were not excluded if they had mixed populations providing the majority were patients with haemorrhagic hypovolaemia resulting from trauma

The inclusion and exclusion criteria were applied independently by two reviewers to all identified citations, and any disagreement resolved by a third reviewer. Where a decision on inclusion or exclusion could not be made on the basis of title or abstract, the full study was retrieved.

Inclusion criteria for systematic reviews for additional research questions:
Systematic reviews of primary evidence of any study design that addressed the questions outlined in section 3.1.1. Two reviewers independently assessed reviews for their relevance.

3.1.3 Data extraction strategy

All identified relevant RCTs were data extracted independently by two reviewers onto pre-piloted data extraction forms. Data on study characteristics, population characteristics, setting, details of intervention and comparator, any additional treatment given and outcomes were extracted. The primary outcome of interest was mortality, although data on short-term and long-term morbidity and quality of life was also extracted.

3.1.4 Quality assessment strategy

Randomised controlled trials
In order to assess the internal validity of the study, the following quality criteria were checked: method of randomisation, unit of randomisation (patients or paramedics); concealment of allocation; follow-up and intention-to-treat analysis; amount of crossover between allocated treatments; similarity of baseline characteristics and comparability of other care received. Blinding was also documented, although it was not considered to be an important quality criterion as individuals administering the treatment cannot be blinded; patients are unlikely to be aware of the different treatment strategies; and the primary outcome of interest (mortality) is unlikely to be influenced by knowledge of a certain treatment.

Systematic reviews
The following checklist was used to appraise the identified systematic reviews. Summaries of outcome data were limited to mortality.

Checklist for Appraisal of Systematic Reviews

- Main characteristics (population, intervention, comparator, outcomes)
- Date of completion of searches
- Search strategy (databases used, language restrictions, citation searching, handsearching)
- Types of studies included (RCTs only, observational studies included)
- Inclusion and exclusion criteria (clearly defined, applied by more than one reviewer)
- Data extraction (performed independently by more than one reviewer)
- Quality assessment (was it performed, what were the criteria)
- Quantity of studies identified
- Synthesis of results (were results pooled, was clinical or statistical heterogeneity assessed, sub-group analyses)
- Direction of effect
- Potential publication bias
- Summary (key findings and validity)

Observational studies

Observational studies were appraised in terms of the following criteria:

Checklist for appraisal of observation studies

- Study design (prospective, retrospective)
- Patient sample (e.g. consecutive, random)
- Baseline characteristics
- Potential selection biases (leading to differences in patient groups being compared)
- Adequacy of analysis and explicit consideration of confounders
- Consistency of conclusion with results of study

3.2 Results

The evidence identified for this report and the evidence underpinning existing UK guidelines will be presented in the context of these guidelines. A full copy of the Consensus Statement (with all references) and extracts from the JRCALC guidelines can be found in Appendix 1 and Appendix 2.

Beyond the primary research question of this assessment, additional key questions, which complicate the interpretation of the primary question are the effect of ALS versus BLS, particularly regarding cannulation and time delay, and the choice of different fluids. Evidence sought by the authors was limited to randomised controlled trials and systematic reviews for the primary research question and systematic reviews for additional questions of interest. Where observational studies have been quoted in the Consensus Statement, these have been appraised. Individual animal studies cited in the Consensus Statement have not been critiqued as we had access to a high quality unpublished systematic review on this topic to provide a less biased perspective. The limited evidence base cited in the JRCALC guidelines has not been listed separately, as it is contained within the Consensus Statement evidence.

3.2.1 Quantity of evidence identified

3.2.1.1 Fluid resuscitation

Randomised controlled trials
Two RCTs were identified that compared immediate with delayed pre-hospital fluids in trauma patients (Bickell, 1994[26], Turner, 2000[27]). Two further potentially relevant RCTs were identified that provide some evidence on the effect of administering different volumes of the same fluid. One of these trials (Dutton *et al*, 2002[28]) compared two resuscitation protocols (to 70mmHg versus >100 mmHg) and the other (Dunham *et al*, 1991[29]) compared two infusion systems (Rapid Infusion System™ versus conventional infusion system).

Systematic reviews
Two systematic reviews were identified: a Cochrane review of fluid resuscitation, where searches were last updated in 2000 (Kwan *et al*, 2003[30]) and an at the time unpublished systematic review of animal models (Mapstone *et al*, in press[31]).

3.2.1.2 Other issues

Systematic reviews addressing the following issues were identified:

A - time delay and early cannulation as aspects of advanced versus basic life support (ALS vs BLS)

C - the choice of fluids administered.

No systematic reviews were identified on the other questions of interest:

B - effect of fluid replacement for different types of injuries (e.g. blunt, penetrating)

D - effect of fluid replacement in paediatric trauma patients

E - ability of paramedics to accurately diagnose hypovolaemia at the scene

F - effect of naturally occurring physiological shock mechanisms and interaction with fluid resuscitation).

A - Cannulation and time delay (ALS vs BLS)

Two systematic reviews investigating the effectiveness of Advanced Life Support (ALS) versus Basic Life Support (BLS) were identified (Liberman *et al*, 2000[32] -searches completed 1998 and Sethi *et al*, 2003[33] -searches completed 2000). One RCT, Nicholl *et al*, 1998,[16] was identified in the review by Sethi *et al*, 2003.[33] This was the only RCT comparing ALS and BLS found.

C - Choice of fluids administered

Ten systematic reviews comparing colloids and crystalloids, or different types of crystalloids or colloids were identified (Alderson *et al*, 2003[34] -searches updated 2000, Alderson *et al*, 2003[35] -searches updated 2001, Bissoni *et al*, 1991[36] -search completion date not stated, Bunn *et al*, 2003[37] -searches completed 2001, Bunn *et al*, 2003[38] -searches completed 2000, Choi *et al*, 1999[39] -searches completed 1996, Schierhout and Roberts, 1998[40] -searches completed 1997, Velanovich *et al*, 1989[41] -search completion date not stated, Wade *et al*, 1997[42] -search completion date not stated and Wilkes & Navickis, 2001[43] -searches completed 2000).

It should be noted that Cochrane reviews are cited using the data of the currently available version, hence all Cochrane reviews are dated 2003. The date of when searches were completed has been added to assess how up-to-date the reviews are.

Submissions from industry and other organisations

1. British Association for Immediate Care (BASICS): statement regarding the role of clinicians in pre-hospital trauma care; no evidence was listed.

2. Joint Royal Colleges Ambulance Liaison Committee (JRCALC): extracts from JRCALC guidelines for fluid administration; the RCTs by Bickell (1994),[26] Turner *et al*(2000)[27] and the systematic review by Alderson *et al* (2003),[34] all of which are discussed in this report, are cited; no additional relevant evidence addressing the primary research question was cited.

3. Faculty of Pre-hospital Care of the Royal College of Surgeons of Edinburgh: extracts from Consensus Statement (see Appendix 1); no evidence was listed.

4. Submissions by Fresenius Kabi Ltd regarding HyperHAES®; the evidence cited referred mainly to comparisons of different types of fluids or animal studies; no additional evidence in the form of RCTs or systematic reviews on the primary research question (early versus

delayed fluid replacement of the same fluid, or administrations of different volumes of the same fluid in trauma patients) was cited.

Flowcharts of the study identification process are shown below in Figure 1 and Figure 2.

Figure 1 Flowchart of study identification: RCTs

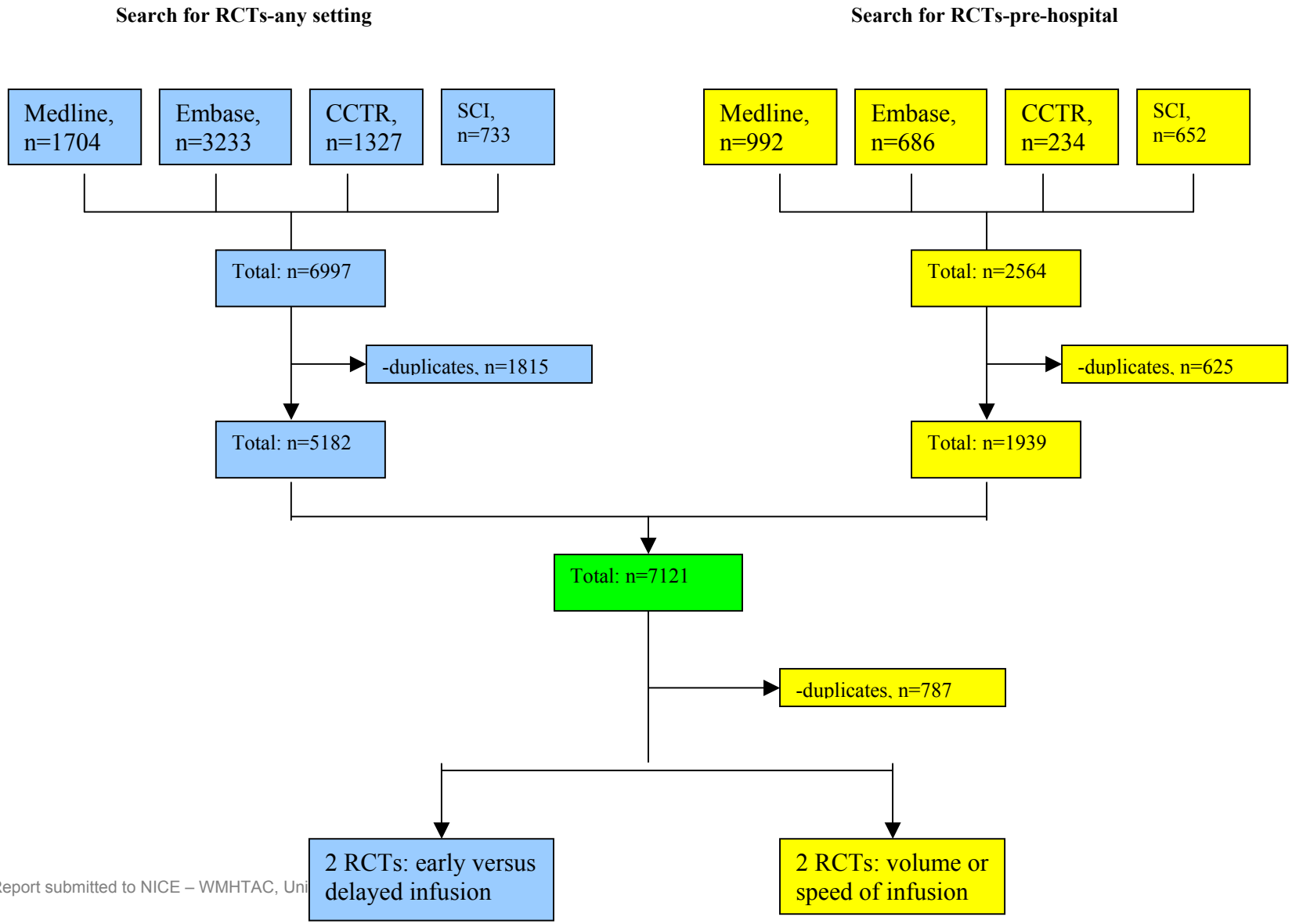
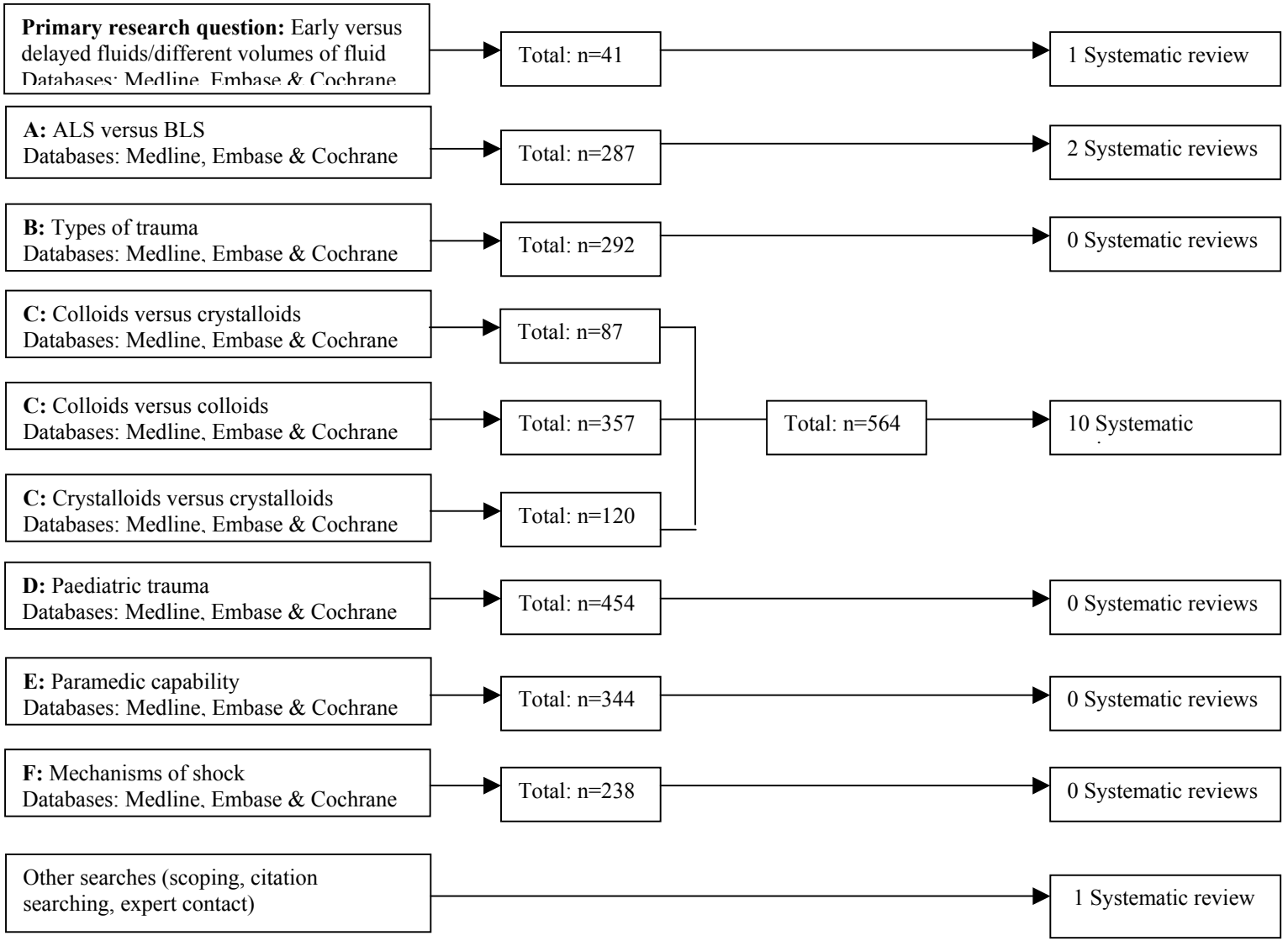


Figure 2 Flowchart of study identification: systematic reviews



3.2.2 Quality of available evidence and assessment of effectiveness

3.2.2.1 Fluid resuscitation (primary research question)

Consensus View
"Fluid should not be administered to trauma victims prior to haemorrhage control if a radial pulse can be felt. Judicious aliquots of 250 mls should be titrated for other patients. If the radial pulse returns, fluid resuscitation can be suspended for the present and the situation monitored. In penetrating torso trauma the presence of a central pulse should be considered adequate. In children less than 1 year old, the use of a brachial pulse is more practical as it is easier to feel."

Extract from JRCALC guidelines:
"Current international research has show little evidence to support the use of Pre-Hospital IV infusion routinely in trauma patients. In cases of penetrating chest and abdominal injuries and aortic aneurysm dissection, an actual ***decrease in survival*** *has been associated with pre-hospital fluid administration. This clashes with previously held views that IV infusion was both essential and life saving in trauma. The logic however, is that after severe haemorrhage, blood pressure drops, blood loss slows right down and fragile clots begin to form.*

If IV fluids are given excessively, these fragile clots will be displaced and re-bleeding occurs. As a rule therefore, ***IV infusions should be commenced en route to hospital,*** *and only sufficient fluid given to maintain a systolic BP of 80-90 mmHg, - equivalent to the return and maintenance of a radial pulse. i.e. if SBP is already 90 mmHg, commence fluid, but at a keep vein open (TKVO) rate, and* ***keep reassessing.*** *However, in cases where there is delay in reaching hospital, IV fluid therapy may be of more benefit. The emphasis therefore is on obtaining IV access while making a more considered judgement on the need to commence IV infusion. In cases of penetrating trauma IV access should be obtained en route to hospital but fluids should be withheld unless absolutely necessary."*

Evidence base for Consensus Statement:
The authors draw on several animal studies, which indicate that aggressive fluid use may be detrimental to outcome. Early animal experiments suggested that fluid replacement improved outcome, however these studies were not based on models of uncontrolled haemorrhage. Later animal studies attempted to replicate uncontrolled haemorrhage more closely and found that bleeding and mortality increased if fluid was administered before bleeding was controlled. In terms of resuscitation strategies, further animal studies suggest that a strategy of hypotensive resuscitation without withholding fluids altogether may be the most effective. There is ongoing discussion about what level of hypotension can be tolerated in humans.

The authors further cite the RCT by Bickell *et al,* 1994[26] (described in **Evidence identified for this report** in this section, below) and one retrospective observational study by Sampalis *et al*, (1997).[44] The latter study was suggestive of a higher degree of mortality being

associated with patients who were given fluids on scene and those who experienced a long time delay. The study provides no evidence to support the use of IV fluids, however, due to the differences between the two groups and the possibility of uncontrolled confounders it is not possible to judge whether fluids are doing harm. Table 4 shows the main characteristics of the study by Sampalis *et al* (1997).[44] Full details of the appraisal can be found in Appendix 4.

Table 4 Observational study: early or delayed fluid administration

Study	Main characteristics	Direction of effect (mortality)	Validity
Sampalis *et al* (1997)[44]	**D:** Retrospective cohort study **P:** Patients with a Pre-hospital Index (PHI) at the scene >3 transported alive to hospital **I:** IV fluids given pre-hospital **C:** No IV fluids given pre-hospital **O:** Mortality (during first 7 days after admission for injury)	After adjustment for confounders (age, sex, ISS, mechanism of injury, pre-hospital time), the use of IV fluids at the scene was associated with a significant increase in mortality; for pre-hospital times <30 minutes, fluids provided no benefit and for longer times pre-hospital fluids were associated with increased risk of mortality	Despite patients being matched by PHI, there were significant differences between the two groups regarding age, ISS, mechanism of injury and body regions injured (all predictors of trauma related mortality); there were more severely injured patients in the IV fluids group; adjusting for known confounders reduced the crude odds of dying from IV fluid replacement from 8.6 (3.4-21.7) to 2.33 (1.02-5.28); it is possible that if unknown confounders were taken into account that the odds would be further reduced; the adjusted odds ratio for a pre-hospital time of less than 30 minutes showed no significant effect from fluid replacement; this study is suggestive of pre-hospital IV fluids not being beneficial and in conjunction with a long time delay being harmful; the use of pre-hospital IV fluids is not supported, although further, less confounded, evidence would be necessary to provide a definitive answer
Overall conclusion: Suggestive of IV fluids being harmful in conjunction with a long time delay, although confounding makes study impossible to interpret; no evidence that IV fluids are beneficial			

D: design of study, P: population, I: intervention, C: comparator, O: outcomes

Evidence identified for this report:
Two RCTs comparing immediate versus delayed fluid replacement in a pre-hospital setting were identified (Bickell *et al*, 1994[26] and Turner *et al*, 2000[27]). Two further RCTs were identified, which compared resuscitation to different blood pressures (Dutton *et al*, 2002[28]) and resuscitation using different infusion systems, rapid and conventional (Dunham *et al*, 1991[29]).

Table 5 shows a summary of the most important features of the studies. Full details on the main study characteristics, study quality and outcomes are listed in Appendix 6.

Table 5 Summary of included studies

Study	Trial design	Population	Main outcomes	Validity of study
Bickell *et al*, 1994 [26]	Parallel RCT; fluids delayed until surgical intervention or given before (pre-hospital and trauma centre)	598 patients aged 16 and over with penetrating injuries and SBP</=90 mmHg; exclusions: RTS of 0 or minor injuries; retrospective inclusion criteria	Significant reduction in overall mortality and hospital days in delayed fluids group; trend towards fewer post-operative complications and lower mortality before reaching operating room; follow-up until discharge (no long term follow-up)	Methods of randomisation appropriate; no concealment possible as randomisation was by day; exclusion criteria appropriate; good compliance; ITT not possible with this trial design as all patients effectively randomised and inclusion/exclusion criteria applied retrospectively; not clear if there was a difference in surgical interventions administered or whether this could have an effect on survival
Overall conclusion: Suggestive of IV fluids being harmful in trauma patients with penetrating injury; some evidence of harm, no evidence of benefit				
Turner *et al*, 2000[27]	Parallel RCT; fluids withheld until arrival at hospital (unless likely to be >1 hour) or given to those patients who would normally have received them	1309 patients aged 16 over, majority with blunt injuries, who were considered likely to benefit from fluids (retrospective inclusion criteria: those who subsequently died, were admitted to ICU or died within 6 months)	No significant differences between delayed and immediate fluid groups in terms of mortality, complications, length of stay or quality of life	Methods of randomisation appropriate; no concealment as cluster randomisation used; not clear if inclusion/exclusion criteria appropriate; good attempt made to include all eligible patients (loss to follow up of 5%); very poor compliance with protocol: only 30.9% in the immediate fluids group received pre-hospital fluids and 79.8% in the delayed fluids group had fluids withheld; if include fluids received before theatre, number in each group receiving fluids are very similar (49.1% and 42.1%); comparison between groups therefore likely to be meaningless; ITT not possible with this trial design as all patients effectively randomised and inclusion exclusion criteria applied retrospectively
Overall conclusion: Insufficient evidence of either harm or benefit of IV fluids				
Dunham *et al*, 1991[29]	Parallel RCT; patients randomised to Rapid Infusion System™, which uses a single catheter for infusion, or a conventional infusion system (which uses several catheters)	36 patients aged 14-60 admitted with evidence of hypovolaemia (SBP<90Torr); types of injury not specified; patients unlikely to survive (GCS<5) excluded	No significant differences in mortality reported, but from raw data mortality appears higher on RIS; trend towards shorter length of stay and fewer complications in those who had the Rapid Infusion System™ and who survived for more than 12 hours	No details on randomisation, concealment or compliance; not clear if all eligible patients enrolled; no ITT for overall analysis (although can calculate for overall deaths); not clear whether any pre-hospital treatment given before arrival in trauma centre; not clear if there were differences in surgical interventions; different interventions not limited to active bleeding period (although more fluids infused during first hour with the Rapid Infusion System™); cut-off point for recording deaths not clear; no power calculation
Overall conclusion: Insufficient evidence of harm or benefit of rapid infusion (trend towards rapid infusion being harmful)				
Dutton *et al*, 2002[28]	Parallel RCT; patients randomised to target SBP of 70mmHg or >100mmHg	110 patients presenting from scene of traumatic injury, evidence of ongoing haemorrhage,	No difference in mortality.	No details on randomisation, concealment or compliance; not clear if all eligible patients enrolled; not clear whether any pre-hospital treatment given before arrival in trauma centre; not clear if there were differences in surgical interventions; not clear if there was a

		SBP<90mmHg; around half with blunt and half with penetrating injuries		difference in fluid volumes administered to groups (based on different blood pressures); cut-off point for recording deaths not clear; no power calculation
Overall conclusion: Insufficient evidence to suggest benefit or harm of resuscitation to different blood pressures				

Included studies

Bickell *et al*, 1994[26]

Main characteristics
This study included patients with penetrating injury and a systolic blood pressure of below 90mmHg. Fluids were either delayed until surgical intervention in the hospital or given before surgical intervention, either in a pre-hospital setting or at the trauma centre. Patients were followed up until they died or were discharged alive. Main outcomes were mortality, complications and length of stay.

Treatments were allocated by day, reflecting the difficulty of operating a per-patient randomisation procedure in this clinical setting. As all patients were included or excluded according to pre-defined criteria, this departure from standard research practice should not in itself bias allocation to treatment groups. There might, however, be some problems arising from retrospective assessment of eligibility. Of 1069 patients with hypotension and penetrating injuries to the torso, 172 (16%) were excluded with a Revised Trauma Score of zero on initial evaluation by paramedics. A further 299 (28%) were excluded because they were found to have minor injuries that did not require major surgical intervention. Characteristics of the remaining patients were well balanced between the two groups.

Outcomes
41/309 (13%) of those resuscitated died before reaching the operating room, compared to 29/289 (10%) in the delayed group. There was a statistically significant reduction in overall mortality (until discharge) for those in the delayed group, with 70% vs 62% surviving (p=0.04). The delayed fluids group had significantly fewer hospital days and there was a non-significant trend towards fewer post-operative complications. There is no data on longer-term outcomes such as morbidity or quality or life in the two groups.

Quality and validity
Methods of randomisation were appropriate to the clinical circumstances, although more details about excluded patients and the decision to include/exclude would be helpful. Patients were drawn from a consecutive sample. Exclusions were on the basis of a Revised Trauma Score of 0 (combination of Glasgow Coma Scale value of 3, SBP of 0 and respiratory rate of 0) and those with minor injury not requiring operative intervention. It seems reasonable to exclude these patients, as they are unlikely to benefit from fluids. A survival rate of 0.027 is associated with a Revised Trauma Score of 0, and all patients in this group subsequently died. All patients excluded with minor injuries subsequently survived. The numbers of excluded patients are not stated for each group but were said to be similar. Baseline characteristics of included patients in the two groups were similar. There was no loss to follow-up after randomisation. Compliance with the protocol was good with 22/289 (7.6%) patients in the delayed fluids group transiently receiving fluids, and fluids not withheld from any patients in the immediate resuscitation group.

Fluids were restricted in the delayed fluids group until arrival in the operating room. It is not stated whether any additional interventions were administered in the time between arrival at the trauma centre and arrival in the operating room (44+/-65 minutes for the delayed group and 52+/-99 minutes for the immediate group). Similar amounts of fluids were administered to both groups in the operating room, although there was a trend for less blood loss during

surgery for the delayed group (p=0.11) with a related lower use of packed red cells in the delayed group (p=0.07). It is not clear if there was a difference in the type of surgical interventions administered to the two groups or whether this could have an effect on survival. Patients were followed up until they either died during hospitalisation or were discharged alive. This length of follow-up may have been insufficient to capture longer-term effects of trauma on mortality. There is no data on later morbidity or mortality. A power calculation estimating the number of patients necessary to see a difference in effect was performed.

Overall, this is a good quality trial and the data appear to have been analysed appropriately. Methodological concerns are minimal and reflect the problems of conducting research in this setting. It should be noted that the patient population was restricted to those with penetrating trauma, and so the results may not be applicable to the majority of cases in the UK.

Turner *et al*, 2000[27]

Main characteristics
A cluster-randomised design was used, with paramedics randomised to different trauma protocols, reflecting the difficulty of individual patient randomisation in this setting; paramedics were 'crossed over' to the other protocol halfway through the trial. Patients were retrospectively excluded on the basis of their injury and some other criteria (dead at scene, minor injuries, burns, certain fracture types, involvement in 'major accidents' urgent GP referrals, helicopter transfers). Patients were included based on subsequent outcomes (length of hospital stay, ICU admissions, died in transit or died within 6 months). The vast majority of patients had blunt injuries. Fluids were either withheld until arrival at hospital (unless transfer time was likely to exceed 1 hour) or given to those patients who would normally receive fluids under current paramedic procedures, although the decision whether or not to initiate fluids remained that of the individual paramedic. Mortality was recorded up to 6 months. Other outcomes were change in Triage Revised Trauma Score, complications, length of stay, admissions to ICU and quality of life.

Outcomes
There were no significant differences between the delayed and immediate fluid group regarding mortality, complications, length of stay or quality of life (mental health scored significantly better in the delayed fluids group).

Quality and validity
Methods of randomisation appear appropriate (the power calculation is based on cluster randomisation, although it is not clear whether the correct methods for analysing a cluster trial were used throughout, or how the 'crossover' aspect of the trial was dealt with). Slightly more patients were randomised to protocol A (immediate fluids) in the second part of the trial (where paramedics crossed over). Reasonable attempts were made to include all eligible patients, 5% of eligible patients were subsequently not included due to missing data. Attempts were made to include only those patients who as part of their pre-hospital management would normally have received fluids and where fluids may influence the outcome. Excluded patients were amongst others those with minor injuries, isolated fractures (neck of femur or single pubic rami fracture) or who were dead at the scene. The inclusion/exclusion criteria applied are not particularly clear, and there might be some concern as to how these were applied.

The main concern, however, is that the inclusion criteria are exclusively based on outcomes (death and length/type of hospital admission). This is likely to cause substantial bias in patient selection, whilst being inefficient at selecting a patient group of interest (there is no mention of hypotension or shock, for example).

Compliance with the protocol was poor: only 30.9% in the immediate fluids group received pre-hospital fluids and 79.8% in the delayed fluids group had fluids withheld. The reason some of these patients were given fluids is due to a long transfer time (> 1 hour). The majority of paramedics therefore did not comply with protocol A (immediate fluids) and only approximately 10% more patients in the immediate fluid group compared to the delayed fluids group received fluids. The reason for withholding fluids in so many of the immediate resuscitation group is not clear, but this will clearly substantially dilute any differences between the groups. In some cases (but not the majority) it was due to a doctor being on the scene or the hospital being very close to the scene of the accident. The problem may have been due to case mix; although certain types of minor injury are excluded, it is not clear that the inclusion criteria do adequately specify patients who would be considered for resuscitation in normal practice (i.e. no mention of hypotension).

A power calculation estimating the number of patients necessary to see a difference in effect was performed. Baseline characteristics of the two groups were similar, and similar amounts of fluids were given to both groups in A & E and pre-theatre. It is not clear if the intention was to withhold fluids in the delayed group until definitive (surgical) intervention. An additional 22% in the delayed fluids group received fluids in the A& E department. The proportions of patients in both groups receiving fluids before theatre (and possibly in the active bleeding phase) were therefore 49.1% (immediate fluids group) and 42.1% (delayed fluids group). Comparisons between the two groups in terms of effectiveness of delaying or withholding fluids are therefore likely to be meaningless.

There are a number of uncertainties surrounding the methodology and analysis of this trial, however in view of the fact that further information would have made very little difference to the ability to draw conclusions on the clinical effectiveness, the authors were not contacted.

Dunham *et al*, 1991[29]

Main characteristics
This study was performed in patients admitted to hospital directly from the scene, who had evidence of hypovolaemia and a systolic blood pressure below 90 Torr (NB this is the unit used by the authors, mmHg is conventionally used). The nature of the injuries sustained is not described. On arrival at hospital, patients were randomised to either the Rapid Infusion System™, which uses a single catheter for infusion, or a conventional infusion system (which uses several catheters). Main outcomes were mortality, complications, days in intensive care and cost. The cut-off point for recording deaths was not specified.

Outcomes
There were no significant differences between those who received rapid or conventional infusion in terms of acute deaths (up to 12 hours), late deaths (post 12 hours) or total deaths. There was a trend towards fewer complications and shorter length of stay in those who

survived 12 hours and received fluids via the rapid infusion system (statistically significant for pneumonia).

The reporting of the trial however obscures the fact that there was a slightly higher overall mortality in the rapid infusion group (5/16 vs 5/20). Although similar numbers of deaths occur in both groups, it is interesting to note that in the RIS group all deaths occurred in the first four hours, while in the other group all deaths occurred after 4 hours (3 in hours 6-12 and 2 on days 3 and day 6 respectively). Whilst this could be a chance finding, a possible explanation could be that RIS increases the risk of death from massive haemorrhage while decreasing the risk of death from the consequences of hypovolaemic shock.

Quality and validity
No details on the randomisation method or method of concealment were given. It was not specified whether an attempt was made to include all eligible patients. Similarly, there were no details on compliance with the protocol or crossover. Patients were excluded with a GCS<5, as they were thought to have little or no chance of survival. The overall analysis excluded those patients who did not survive the first 12 hours, however the total number of deaths was listed for all patients. There was some difference in baseline scores (the authors imply that patients in the rapid infusion group may have been worse off to begin with), although it is not clear whether these differences were clinically significant. As there were only 36 patients in total it is possible that randomisation may not have produced groups that were totally comparable. No power calculation estimating the number of patients necessary to see a difference in effect was included. It is not clear whether patients received any treatment prior to arriving at the hospital, similarly it was not clear whether there were any differences in surgical interventions between the two groups. The different interventions (rapid and conventional infusion) appeared not to be limited to the active bleeding period, but were continued for at least 24 hours. The cut-off point for recording deaths was not clearly specified.

The most important criticism of this trial report is that the results presented obscure the fact that, if anything, mortality appears to be higher in the RIS group and that the RIS deaths all occur early on, during the period where pre-hospital care might be expected to have a negative influence on survival. The trial itself is too small to provide substantial information either way, but the results do not appear to support RIS.

Dutton *et al*, 2002[28]

Main characteristics
This randomised trial compare different levels of aggressiveness of resuscitation. It was performed in patients presenting directly from the scene of traumatic injury with evidence of ongoing haemorrhage and a systolic blood pressure of less than 90 mmHg. Around half the injuries were blunt and half were penetrating injuries. Fluids were administered to achieve either a target blood pressure of 70mmHg or a target blood pressure of 100 mmHg or more. The outcome measure was mortality, although the cut-of point for recording death was not clearly stated. It should be noted that the inclusion criteria of BP <90 mmHg would imply that less patients received fluids in the cautious resuscitation group than in the more aggressive resuscitation group.

Outcomes
The same number of deaths occurred in both groups. Other outcomes were not recorded.

Quality and validity
There were no published details on the randomisation method or method of concealment. However contact with the authors by the Injury Group of the Cochrane Collaboration established that *"Subjects were randomised by drawing the next numbered envelope from a batch of twenty thoroughly mixed but sequentially numbered envelopes kept in the the Trauma Unit. The physicians caring for the patients did not know the group allocation until after the patient was randomised."* (Kwan, personal communication) It is not clear whether all eligible patients were enrolled (it is stated that patients were enrolled after giving consent, but is not clear if all eligible patients were asked for consent, or what happened to those patients who could not give consent or who declined). There are no details on loss to follow up, similarly there are no details on compliance or crossover. There were some slight differences in baseline characteristics, it is not clear whether these were clinically significant. It not specified whether patients received any interventions before arrival at the hospital, or if there was a difference in surgical interventions performed in the two groups. The actual fluid volumes given to the two groups are not stated, although an assumption could be made that more fluid would be given to the group where the intention was to maintain a higher blood pressure. The cut-off point for recording deaths was not clearly stated. There is no indication that a power calculation estimating the number of patients necessary to see a difference in effect was performed.

Other systematic reviews
Two relevant systematic reviews were identified. Kwan *et al* (2003)[30] concerns the timing and volume of fluid replacement in trauma patients, the systematic review by Mapstone *et al*(in press)[31] of fluid resuscitation using animal models. Table 6 lists the main characteristics of the systematic reviews. Details of the full appraisals can be found in Appendix 5.

The review by Kwan *et al* (2003)[45] includes the same four RCTs as identified for this report. The authors include two additional RCTs: Blair *et al* (1986)[46] compared early versus delayed blood transfusion in patients with acute gastrointestinal haemorrhage during the first 24 hours of admission. There was no statistically significant difference in mortality between the two groups. Fortune *et al* (1987)[47] compared the maintenance of haematocrit at 30% and 40% with blood transfusion in patients following acute injuries and haemorrhage during the first 72 hours of admission. There were no deaths in either group. These studies were not included in this report as blood has different properties compared to crystalloid and colloid fluids and would not be the fluid of choice for pre-hospital treatment of trauma patients as it cannot be easily carried by ambulances. The authors conclude that there is no evidence to support the use of early or large volume intravenous IV fluid administration and that there is uncertainty about the effectiveness of fluid resuscitation in patients with bleeding. This is in keeping with the findings of this report.

The systematic review by Mapstone *et al* (in press)[31]based on animal models found differences in the effect of fluid on mortality depending on the haemorrhage model used, and a reduction in the risk of death with hypotensive compared to normotensive resuscitation (see Table 6 for details). (This was a more complete version of the same systematic review published in the BMJ.[45]) The way that animal models relate to human injuries is however unclear.

Table 6 Summary of systematic reviews of fluid delay/volume

Study	Main characteristics	Direction of effect (mortality)	Validity
Kwan *et al*, 2003[30] (searches completed 2000)*	**P:** Patients with haemorrhagic hypovolaemia of traumatic or non-traumatic origin **I:** Any type of intravenous fluids (including blood)-early administration **C:** Same type of intravenous fluids-later administration or different volume **O:** Mortality	Early versus delayed fluids: there was a statistically significant difference favouring delayed fluids for one study in patients with penetrating injury (Bickell 1994); there were no significant differences in the other two studies (Turner 2000, Blair1986) Different volumes of fluids: there were no significant differences for mortality in the two studies where deaths occurred (Dutton 2000, Dunham 1991); there were some methodological flaws in the studies	This appears to be a well conducted review and it is unlikely that relevant studies were missed; there is some clinical heterogeneity as studies relate to both pre-hospital and hospital settings and there are some methodological flaws in the studies; the authors found no evidence from randomised controlled trials to support the use of early or large volume IV fluid administration in uncontrolled haemorrhage
Overall conclusion: no evidence to support the use of IV fluids in uncontrolled haemorrhage			
Mapstone *et al* (in press)[31]	**P:** Animal models of uncontrolled haemorrhage **I:** Fluid resuscitation (any fluid)-early **C:** Fluid resuscitation (same fluid)-delayed or different volume **O:** Mortality	There was no statistically significant difference in mortality according to early or delayed fluids (risk ratio=0.88, 0.73-1.07, trend towards favouring fluids); there was a statistically significant difference in mortality favouring fluids for the aortic injury and >50% tail resection in rats sub-groups, and for studies where blood loss volume was reported; there was a statistically significant difference in mortality favouring no fluids for the <50% tail resection in rats and other vessel injury sub-groups as well as for the sub-group where volume of blood loss was not reported; there was a statistically significant difference in mortality favouring hypotensive resuscitation	This appears to be well conducted review and it is unlikely that relevant studies were missed; there is uncertainty around the relevance of randomisation and allocation concealment for the quality assessment of animal studies (only two studies described how animals were divided into treatment groups); there was a large amount of heterogeneity in the effect of fluid resuscitation on the risk of death, much of which was explained by the type of haemorrhage model used; fluid resuscitation appears to reduce the risk of death in animal models of severe haemorrhage, but increases the risk of death on those with less severe haemorrhage; hypotensive resuscitation reduced the risk of death (based on 9 trials); the results of this study cannot necessarily be extrapolated to humans
Overall conclusion: no conclusions regarding fluid use in humans possible; further investigation of acceptable blood pressure targets may be appropriate			

*an updated version is being prepared for the Cochrane library; the author has kindly made the draft available; no further studies were identified; one trial which is reported as ongoing in the current version now competed (Dutton, 2002); this does not change the conclusions of the review; 4/6 identified studies, excluding those relating to blood transfusion, are discussed in detail in this review (Bickell 1994, Turner 2000, Dunham 1991 and Dutton 2002).

Conclusion: quantity of fluids

Few definitive conclusions can be drawn from the evidence identified. The study by Bickell *et al* (1994)[26] is the most methodologically sound (see Table 5). The study showed a significant benefit from delaying fluids, and whilst there may be some uncertainty surrounding this evidence, it would not be possible to conclude that pre-hospital fluid resuscitation is beneficial. It should be noted that the population in this study (with penetrating injuries) is not representative of the majority of trauma patients seen in the UK, who have blunt injuries.

In the study by Turner *et al* (2000)[27] the selection criteria were flawed, resulting in, not only the potential for substantial bias, but also such poor adherence to protocol that there was little difference in terms of intervention and comparator between the two groups. This makes the results extremely difficult to interpret. Mortality was similar in the two groups, which is to be expected given the small difference in fluid use between the groups.

The studies by Dunham *et al* (1991)[29] and Dutton *et al* (2002)[28] relate to the volume of fluids administered; fluids were not withheld at any point in time during these studies.

The study by Dunham *et al* (1991)[29] was methodologically poor (see Table 5). In particular the nature of any pre-hospital treatment is not clear as the study commenced at the trauma centre. It is not clear at which point during the study bleeding was controlled. The authors conclude that the Rapid Infusion System™ is beneficial in terms of coagulopathy, temperature preservation and other physiological parameters, however they do not discuss the fact that there were slightly more deaths overall in the RIS group, or that these occurred earlier than deaths in the control group (this is attributed by the authors to the fact that patients are more seriously injured in the RIS group). The study population of 36 patients was undoubtedly too small to show any potential differences in effect. No conclusions can be drawn as to whether administration of a larger or smaller volume of fluids in the first hour after admission to a trauma centre has any benefits regarding mortality, particularly as it is not clear whether any pre-hospital fluids were given.

The study by Dutton et al (2002)[28] is also methodologically poor (see Table 5). Again, it is not clear whether any pre-hospital treatment was given. The difference in interventions was based on patients being resuscitated to different blood pressures. It was not clear if this was actually associated with different volumes of fluids, although that assumption could be made. The number of deaths in both groups was identical. Therefore no conclusions can be drawn about the relative efficacy of the two resuscitation strategies.

Little additional evidence is provided by the two systematic reviews identified. (Kwan *et al*, 2003[30] and Mapstone *et al* (in press)[31]). The Mapstone study of animal models found that hypotensive resuscitation was more effective compared to normotensive resuscitation, however it is not clear whether this would apply to human injuries.

Although the balance of the evidence suggests no benefit, and possibly actual harm, due to early and/or aggressive fluid resuscitation, it is possible that there are sub-groups of patients who might benefit from more aggressive resuscitation and others who are clearly harmed. Thus whilst adopting the policy which appears to be the least harmful on average is clearly appropriate, outcomes would be optimised if we could identify particular groups for whom resuscitation is clearly indicated or contraindicated. In order to be useful such sub-groups

would be needed to be readily identifiable in the field and this may not be possible. For example there is some question over diagnostic accuracy of peripheral pulse and carotid pulse palpation as recommended by current guidelines. It is widely cited that a palpable peripheral pulse implies a systolic blood pressure of at least 70-80 mmHg while a carotid pulse a systolic blood pressure of 60-70 mmHg. Despite following up the references given for these statements, none reported empirical studies to support them. Various experts offering their clinical opinion suggested that this "rule of thumb" was very crude and that actual blood pressure would vary greatly from patient to patient depending on other factors (e.g. age). We found a small study that set out to examine how accurate the advanced trauma support guidelines were in predicting blood pressure from palpable pulses.[48] The authors conclude that the findings do not support the teaching on the relation between palpable pulses and systolic blood pressure. However it was based on only 20 patients and is too underpowered to be able to reliably draw such a conclusion. A further study from 1993 looked at 223 patients and concluded that "blood flow cannot reliably be inferred from arterial pressure and heart rate measurements until extreme hypotension occurs".[49]

In conclusion, there is limited evidence from the current research literature to recommend a particular fluid management regime in terms of early or late fluid administration for a given trauma patient. There is no evidence to suggest that early or aggressive resuscitation is beneficial, and some evidence to suggest that it is harmful. It is doubtful whether the current evidence could be used to identify sub-groups of patients for whom resuscitation is more or less beneficial, particularly given that any useful criteria would have to be assessable quickly, and accurately, on scene.

3.2.2.2 Cannulation and time delay (ALS versus BLS)

Consensus View

"Cannulation at an early stage is desirable. However, in most situations, priority should be given to transfer of the patient to a centre where definitive care can be provided. The on scene time should not be prolonged by attempts to gain a line. Intravenous access during transit has been employed success-fully and should be considered where appropriate expertise and training are available. A limit of two attempts en route is reasonable. In cases of entrapment, circulatory access should be gained on scene. This reflects the unique demands of this area of pre-hospital medicine."

Extract from JRCALC Guidelines

"As a rule, ***IV infusions should be commenced en route to hospital,*** *and only sufficient fluid given to maintain a systolic BP of 80-90 mmHg, - equivalent to the return and maintenance of a radial pulse. i.e. if SBP is already 90 mmHg, commence fluid, but at a keep vein open (TKVO) rate, and* ***keep reassessing.*** *However, in cases where there is delay in reaching hospital, IV fluid therapy may be of more benefit."*

Evidence base for Consensus Statement

The Consensus Statement draws on the evidence of four observational studies (see Table 7, full details of the appraisal of these studies can be found in Appendix 4).

The study by Demetriades *et al* (1996)[50] was suggestive of a 'scoop and run' policy being beneficial, as the mortality was higher in patients brought to hospital by paramedics compared to those that were brought in by bystanders, relatives or the police. Known confounders were adjusted for in their analysis, although one likely confounder, time to definitive treatment, was not adjusted for. As the time to treatment in those patients brought in by bystanders etc. is likely to have been shorter, this may have biased the results.

Pepe *et al*, (1987)[51] found that pre-hospital time did not appear to affect survival, although this was based on comparisons of observed and expected survival of very small sub-groups. The groups were likely to have been too underpowered to show any potential effects.

Jacobs *et al*, (1984)[5] found that patients treated by ALS compared to BLS showed a greater improvement in Trauma Score in the pre-hospital phase. This measure is not meaningful as the authors fail to take into account that the absolute Trauma Score was higher in the BLS group at the outset. The authors conclude that ALS has a positive effect on survival, although survival was actually higher in the BLS group. Whilst this may have been due to less severe injuries, no adjusted analysis was performed, which would have allowed a comparison between the groups.

The study by Nicholl *et al*, 1998[16] compared the effect of ambulance crews with ALS and BLS training. The study was originally designed as an RCT, but was analysed predominantly as a cohort study, as randomisation was not successful. Crude and adjusted mortality rates were higher in the paramedic–attended patients. It is difficult to conclude anything from this study due to a number of biases in the design and conduct of the research, particularly the use of outcomes as an inclusion criterion and the large quantity of missing data (especially in the EMT group). A more convincing finding of the study is that paramedics tend to give more interventions on scene and that this is linked to a delay in transferring patients to hospital.

Table 7 Observational studies: cannulation and time delay

Study	Main characteristics	Direction of effect	Validity
Demetriades *et al*, 1996[50]	**D:** Retrospective cohort study **P:** Patients with major trauma (SBP <90mmHg adults, SBP60mmHg children) **I:** transport by paramedics (EMS) **C:** transport by non-paramedics (police, friends etc., non-EMS) **O:** mortality	The crude mortality rate was 9.3% in the EMS group and 4.0% in the non-EMS group, Relative Risk 2.32 (1.67-3.22); statistically differences in mortality between the groups were seen only in patients with an ISS>15; after adjustment for ISS, the Relative Risk was 1.60 (1.18-2.15); the crude mortality rate in patients with an ISS>15 was 28.8% (EMS) and 14.1% (non-EMS); after adjusting for confounding factors, the rates were 28.2% (EMS) and 17.9% (non-EMS), p<0.001	The groups were significantly different in terms of mechanism of injury, GCS, ISS and blood pressure, with the EMS group being more severely injured; the authors adjusted the result for known confounders, however, time to definitive treatment (which is likely to have been shorter in the non-EMS patients) was not adjusted for as this data was not obtainable; there may be additional unknown confounders biasing the results; it is not possible to distinguish between the effects of time delay and the effects of interventions; the results are suggestive of a 'scoop-and –run' policy being beneficial, although further, less confounded, evidence would be necessary to provide a definitive answer
Overall conclusion: suggestive of non-ALS transport being beneficial, results subject to confounding			
Jacobs *et al*, 1984[5]	**D:** Prospective cohort study **P:** severely injured patients with SBP<100mmHg **I:** ALS (consisted primarily of IV fluid administration-88%) **C:** BLS **O:** Change in Trauma Score during pre-hospital care & effect on survival	The authors state that analyses adjusted for the original TS showed that the TS in ALS patients improved more than that of BLS patients and an early change in TS was positively associated with survival, independent of time; they conclude that ALS pre-hospital care has a positive effect on survival	There were significant differences in TS and ISS between the two groups; patients in the ALS group were more severely injured (72% of patients with a TS of 1-3 were in the ALS group); the authors state that there was greater improvement in TS in the ALS patients compared to BLS patients, however it is clear that the average TS was higher to begin with in the BLS group and smaller changes here would not necessarily mean a lower absolute TS (or lower chance of survival); as expected from the severity of injuries, there were more deaths in the ALS group; no attempt was made by the authors to adjust for the type and severity of injuries in order to compare survival rates between the two groups; there is no evidence from this study to conclude that one type of life support is more beneficial than another
Overall conclusion: results uninterpretable; no evidence to suggest that ALS is beneficial or harmful			
Pepe *et al*, 1987[51]	**D:** Prospective cohort study **P:** patients with penetrating injuries and SBP</=90 mmHG **I/C:** different total pre-hospital times (NB: 254 randomly selected patients also had Pneumatic	The authors found no statistically significant differences between predicted survival (using the TRISS methodology) and observed survival in four patient groups stratified by total pre-hospital time and trauma scores	Sub-groups (according to total pre-hospital time and Trauma Score) were determined arbitrarily in order to yield sufficient numbers of patients in each sub-group; these sub-groups were very small and likely to be underpowered; there was a trend towards less observed than predicted survival in TS 7-11 group where there was a larger group (n=102)

	Anti-shock Garments applied) **O:** Survival (discharge alive from hospital)		
Overall conclusion: study likely to have been too underpowered to be able to show a relationship, or the lack of one, between pre-hospital time and death rates			
Nicholl *et al*, 1998[16]	**D:** Originally designed as parallel RCT but analysed as prospective cohort as randomisation was largely unsuccessful **P:** Patients with serious trauma who died or stayed in hospital for more than 3 nights and who were not attended by a doctor on scene **I:** Ambulance crews with ALS training **C:** EMT crews **O:** Mortality, quality of life (SF-36 score), cost	Non-significant trend towards more deaths in the ALS group; crude OR 1.34 (95% CI 0.86-2.11); adjusted OR=1.74 (0.89-3.41) (adjusted for ISS, head AIS, injury mechanism, age, type of incidence, patient trapped or not)	There are a number of biases in the design and conduct of the study relating in particular to the use of outcomes as inclusion criteria and the large proportion of missing data; the contribution of unknown confounders is not considered; no explanation is given of the counter-intuitive inverse relationship between travel time and mortality; the study provides insufficient evidence for potential harm or benefits from paramedic crew attendance; a more convincing finding is that paramedics tend to give more interventions in scene and that is contributes to a time delay
Overall conclusion: the study is too biased to conclude that crews without ALS training are harmful or beneficial to trauma patients			

D: study design, P: population, I: intervention, C: comparator, O: outcome

Evidence identified for this report:

Two relevant systematic reviews were identified. The systematic review by Liberman *et al* (2000)[32] summarises studies comparing advanced or basic life support. The authors reviewed 15 studies containing mortality data and found an increase in rate of mortality in ALS compared to BLS patients. Many of the studies had methodological flaws or a poor study design as assessed by the author. An assessment for clinical or statistical heterogeneity was not performed before results from different studies were pooled. It is likely that there were clinical differences between the studies. Due to the nature of the study designs, confounding factors are likely to bias the results of most studies, although the authors attempt to adjust for known confounders. The review is suggestive of BLS being beneficial, although definitive evidence would need to be sought from less confounded studies.

The systematic review by Sethi *et al* (2003),[33] which limited the search to RCTs, found only one study, Nicholl *et al*, 1998,[16] the cohort analysis of which is discussed above. The RCT analysis of the study included only 16 patients. As the control room was undecided regarding the ethics of randomising paramedic or emergency technician crews to incidents, only 185 patients in total were randomised, of which 16 met their inclusion criteria. Little data is reported for the 16 patients.

Table 8 lists the main characteristics of the systematic reviews. Full details of the appraisals can be found in Appendix 5.

Table 8 Summary of systematic reviews of ALS versus BLS

Study	Main characteristics	Direction of effect (mortality)	Validity
Liberman *et al*, 2000 (searches completed 1998)	**P:** Trauma patients **I:** Pre-hospital ALS **C:** Pre-hospital BLS **O:** Mortality	Based on RCTs and observational studies: 3/15 studies favoured ALS, 12/15 favoured BLS in terms of mortality. The overall crude OR was 2.92 (favouring BLS). Studies with a good design gave an OR 1.89 (favouring BLS to a lesser extent). Confidence intervals were not stated	It is possible that some studies were missed, as the search strategy was not very comprehensive; some of the included studies had poor study designs and weak methodology; there was no assessment of clinical and statistical heterogeneity between studies before they were pooled; overall direction of effect is towards BLS being more effective in preventing deaths than ALS (although it is not clear if this is statistically significant); this effect is less pronounced for studies with higher design quality; it is not clear to which extent confounding in the individual studies is contributing to this result, although the author has attempted to adjust for this
Overall conclusions: No evidence to suggest that ALS is beneficial			
Sethi *et al*, 2003 (searches completed 2000)	**P:** Trauma patients **I:** Ambulance crews with ALS training **C:** Ambulance crews with any other level of training **O:** Mortality	There was a non-significant trend towards an increase in mortality in those patients attended by paramedics compared to those attended by emergency medical technicians	This appears to a well conducted review and it is unlikely that relevant studies were missed; the evidence of increased effectiveness of BLS is obtained from one RCT, Nicholl *et al*, 1998[16], which is discussed above and in Appendix 4.
Overall conclusions: No evidence to suggest that ALS is beneficial			

P: population, I: intervention, C: comparator, O: outcome

Conclusion: cannulation and time spent on scene (ALS versus BLS)

There is insufficient evidence to indicate whether the time delay associated with giving additional interventions has an effect on morbidity and mortality. Observational studies have suggested that poorer outcomes are linked to ALS, which in turn is linked to giving additional interventions and/or a time delay. Observational studies are confounded as it is likely that more time will be spent at the scene and more interventions will be given to patients who are more severely injured (and thus may have a poorer prognosis). It is not possible to determine whether the poorer outcomes are linked to the time delay itself, to the interventions that cause the time delay, to the fact that additional interventions may be undertaken in patients who are more severely injured, the fact that patients were treated differently in different studies or a combination of these factors. Only one RCT of ALS versus BLS was identified and the study was not successfully implemented (only 16 patients of a cohort of 2000 were successfully randomised).

Given that there is some evidence to suggest that delaying definitive treatment produces an adverse outcome, and little evidence to suggest that ALS may be beneficial, the recommendation in the Consensus Statement not to delay transfer is appropriate.

3.2.3 Choice of fluids

Consensus view

"This area continues to be one in which, despite an increasing body of evidence, no consensus regarding choice of fluid has been reached. Broadly, the choice of options includes:

- *no fluid*
- *crystalloids (isotonic and hypertonic)*
- *colloids (mainly gelatins and starch solutions)*
- *oxygen carrying solutions (blood and blood substitutes)*

The decision is a complex one and includes consideration of the factors listed below:

early haemodynamic effects
effects on haemostasis
oxygen carriage
distribution and capillary endothelial leak
modulation of inflammatory response
safety
pH buffering
method of elimination
practicality and cost

Modern perfluourocarbons and haemoglobin-b oxygen carriers are currently still largely experimental. Blood (together with human albumin solution and fresh frozen plasma) is costly and difficult to store, having a relatively short shelf life. In addition, issues regarding compatibility and disease transmission make blood and its derivatives unlikely candidates as a permanent solution in the pre-hospital situation. The debate as to the superiority of crystalloid or colloid continues, several decades after it began. Many recent publications advocating specific solutions, emphasize the heterogeneity within both categories of resuscitation fluids. Resuscitation fluids should be evaluated on an individual basis and not in terms of generic groupings. Isotonic crystalloid solutions are cheap, easy to store and warm and have an established safety record when they are used appropriately. They produce a relatively predictable rise in cardiac output and are generally distributed evenly throughout the extracellular space. They do not draw water out of the intravascular space. The use of Ringers solution as the fluid of choice in burns has been documented. It offers some buffering capacity but carries a possible risk of iatrogenically increasing lactic acidosis, when given in large doses or to patients with liver failure. Saline in large quantities may produce a hyperchloraemic acidosis. The case for hypertonic solutions in head injury has not yet been conclusively established in a randomised controlled trial. A meta-analysis by Wade et al (1997) strongly suggests a survival advantage and such a trial is urgently required. At present, isotonic saline is recommended as the first line fluid in the resuscitation of a hypovolaemic trauma patient."

Extract from JRCALC guidelines

"500ml IV of crystalloid solution should be given, and the effects assessed on the circulatory system, before further fluids are given. The aim is to reduce tachycardia and other features of hypovolaemia, whilst maintaining a ***systolic BP of around 80 - 90 mmHg."***

Evidence base for Consensus Statement:
The Consensus Statement discusses the underlying rationale for choice of different types of fluids by drawing on experiments performed in animals, in vitro studies, studies in healthy volunteers and reviews and comments. The results from these studies give an indication of how different types of fluids could potentially act in trauma patients. The authors then refer to four systematic reviews comparing colloid and crystalloid use in humans (Schierhout *et al*, 1998[40]; Alderson *et al*, 2003[34]; Bunn *et al*, 2003[38] and Choi *et al*, 1999[39]) concluding that resuscitation fluids should be evaluated on an individual basis and not in terms of generic groupings (as was done in the reviews). They do not draw any conclusions from these reviews as to which solutions might be more suitable. They then describe the advantages of isotonic crystalloid solutions drawing on a review of use of this solution in burns. No evidence is cited for the advantages of this type of fluid over others in different types of trauma patients.

Evidence identified for this report:
Ten systematic reviews were identified comparing different types of fluids, including the four listed in the Consensus Statement. A summary of the studies is shown in Table 9. Full details of the appraisals can be found in Appendix 5. Studies are listed in date order by topic.

Table 9 Summary of systematic reviews of fluid choice

	Study	Main characteristics	Direction of effect (mortality)	Validity
Any crystalloid versus any colloid	**Velanovich, 1988[41] (not stated when searches completed)**	**P:** Trauma and non-trauma patients (not defined) **I:** Any crystalloid **C:** Any colloid **O:** Mortality	There was a non significant trend towards crystalloids being more effective in trauma patients	There were few methodological details and it not possible to assess whether the author could potentially have missed relevant studies; there were no details on the study quality, types of crystalloid or colloid, resuscitation protocols, additional interventions or case-mix; it is not possible to conclude whether a specific colloid or crystalloid would of benefit to a particular trauma patient.
	Overall conclusion: no evidence of benefit of a particular fluid in trauma patients			
	Bisonni *et al*, 1991[36] (not stated when searches completed)	**P:** Injured patients with hypovolaemia; patients with surgical stress; patients with pulmonary failure **I:** Any crystalloid **C:** Any colloid **O:** Mortality	There were no statistically significant differences in mortality between the crystalloid or colloid group in injured patients with hypovolaemia	There were few methodological details and it not possible to assess whether the author could potentially have missed relevant studies; there were no details on the study quality, types of crystalloid or colloid, resuscitation protocols, additional interventions or case-mix; it is not possible to conclude whether a specific colloid or crystalloid would of benefit to a particular trauma patient.
	Overall conclusion: no evidence of benefit of a particular fluid in trauma patients			
	Schierhout & Roberts, 1998[40] (searches completed 1997)	**P:** Patients with trauma or burns, sepsis or undergoing surgery **I:** Any crystalloid **C:** Any colloid **O:** Mortality	There was a trend towards crystalloids being more effective than colloids for trauma patients (both for studies with and without adequate concealment), although this was not statistically significant	This appears to be a well conducted review; there were differences in the types of colloids and crystalloids administered and there were differences in clinical parameters such as resuscitation protocols, additional interventions administered and case mix; no firm conclusion can therefore be drawn regarding the advantages of a specific colloid or crystalloid for a particular trauma patient, although there seems to a trend towards crystalloids being slightly more effective overall.
	Overall conclusion: no evidence of benefit of a particular fluid in trauma patients (potential trend towards crystalloid being more effective)			

	Study	Main characteristics	Direction of effect (mortality)	Validity
	Alderson *et al*, 2003[34] (searches completed 2000)	**P:** Patients with trauma or burns, sepsis or undergoing surgery **I:** Any crystalloid **C:** Any colloid **O:** Mortality	For meta-analyses of hydroxyethylstarch versus crystalloid, modified gelatin versus crystalloid, dextran versus crystalloid and dextran in hypertonic crystalloid versus isotonic crystalloid there were no statistically significant differences in mortality; for the meta-analysis of albumin or plasma protein fraction versus crystalloids there was a significant difference in mortality favouring colloid; when one trial with poor allocation concealment was excluded, there was no significant difference; there was a trend for crystalloids to be more effective (compared to albumin/PPF, hydroxyethylstarch and dextran) and colloids to be more effective compared to modified gelatin	This appears to be a well conducted review; however, as specified, there was no analysis for trauma patients only; there was heterogeneity between trials in terms of clinical parameters such as timing of intervention, resuscitation regimens, additional interventions and case-mix; there was a non-significant trend favouring crystalloids (compared to albumin/PPF, hydroxyethylstarch and dextran), however, it is not possible to draw conclusions regarding the effectiveness of specific colloids compared to specific crystalloids in a particular trauma patient
	Overall conclusion: no evidence of benefit of a particular fluid in trauma patients (potential trend towards crystalloid being more effective)			
Isotonic crystalloid versus any colloid	**Choi *et al*, 1999[39] (searches completed 1996)**	**P:** Adults requiring fluid resuscitation **I:** Isotonic crystalloid **C:** Any colloid **O:** Mortality	Significant difference between crystalloids and colloids in the trauma sub-group, favouring crystalloids.	This appears to be a well conducted review; there were some differences in the types of colloids and crystalloids administered and there were differences in clinical parameters such as resuscitation protocols, additional interventions administered and case mix (1 of the 5 trauma studies related to thermal injury); although crystalloids performed significantly better overall, interpretation of this should be undertaken with caution; no firm conclusion can be drawn regarding the advantages of a specific colloid or crystalloid for a particular trauma patient
	Overall conclusion: no evidence of benefit of a particular fluid in trauma patients			

	Study	Main characteristics	Direction of effect (mortality)	Validity
Albumin/PPF versus no albumin or crystalloid	**Alderson *et al*, 2003[35] (searches completed 2001)**	**P:** Patients with hypovolaemia, burns or hypoalbuminaemia **I:** Albumin/plasma protein fraction (PPF) **C:** No albumin /PPF or crystalloid **O:** Mortality	For the sub-group with hypovolaemia (studies with or without adequate concealment) there was a statistically non-significant higher risk of death with albumin	The review appears to have been well conducted, although studies with fairly heterogeneous patient groups have been pooled; the majority of studies included in the hypovolaemia sub-group are in patients undergoing surgery; within the three studies with trauma patients in this group there were differences in clinical parameters such as resuscitation protocols, additional interventions and case mix; no conclusions can be drawn regarding the effectiveness or harm of albumin for a specific type of trauma patient.
	Overall conclusion: no evidence to support the use of albumin over another fluid in trauma patients			
	Wilkes & Navickis, 2001[43] (searches completed 2000)	**P:** Any patient requiring albumin **I:** Albumin **C:** No albumin, a lower dose of albumin or crystalloid **O:** Mortality	There was a non-significant tend for the control (no albumin, a lower dose of albumin or crystalloid) to be more effective in surgery and trauma patients; neither of the two trials in trauma patients showed a significant effect in either direction; the authors found evidence of small trial bias, with no significant effect if analysis was limited to trials with over 100 patients	This appears to a well conducted review; it is unlikely that relevant studies were missed; only two included trials referred to trauma populations only; there are differences in clinical parameters such as case mix, additional interventions and fluid administration protocols; no conclusion can be drawn regarding the effectiveness of albumin versus no albumin/less albumin or crystalloid in trauma patients
	Overall conclusion: no evidence to support the use of albumin over another fluid in trauma patients			
Hypertonic crystalloid with or without dextran versus isotonic crystalloid	**Wade *et al*, 1997[42] (not stated when searches completed)**	**P:** Patients with traumatic injury and SBP<100 mmHg **I:** 250ml hypertonic (7.5%) saline (HS) with or without 6% dextran 70 (HSD) **C:** 250ml of isotonic crystalloid **O:** Mortality	There was no statistically significant difference between HS and isotonic crystalloid regarding mortality; there was no statistically significant difference between HSD and isotonic crystalloid regarding mortality, although there was a slight trend towards HSD being more effective (in 7/8 studies)	This appears to a well-conducted review; there were no significant differences between the fluid regarding mortality, although there was a slight trend towards HSD being more effective; there were some sources of clinical heterogeneity (mode and extent of injuries, timing of fluid administration, i.e. pre-hospital or hospital) although the included populations are more homogenous than in the other reviews; in all cases additional isotonic therapy was given as per centre policy-the effect of this is uncertain; no conclusions can be drawn regarding the effectiveness of a specific fluid in a given trauma patient, although a potentially beneficial effect of HSD in some patients cannot be ruled out
	Overall conclusion: no evidence of benefit of a particular fluid in trauma patients (potential trend towards HSD being more effective)			

	Study	Main characteristics	Direction of effect (mortality)	Validity
Isotonic crystalloid versus hypertonic crystalloid	**Bunn *et al*, 2003[37] (searches completed 2001)**	**P:** Patients with trauma, burns or undergoing surgery **I:** Hypertonic crystalloid **C:** Isotonic crystalloid **O:** Mortality	There was no statistically significant difference in mortality between hypertonic and isotonic crystalloid (trend towards hypertonic being more beneficial) in trauma patients;	This appears to be a well conducted review; based on 6 trials, there appears to be no significant difference between hypertonic and isotonic crystalloid; there was heterogeneity between the trials regarding clinical parameters such as timing of intervention (pre-hospital and hospital), additional treatments given, case mix; no conclusion can be drawn as to the benefits of one fluid over another for a particular trauma patient.
	Overall conclusion: no evidence of benefit of a particular fluid in trauma patients (potential trend towards hypertonic crystalloid being more effective)			
Colloids versus different classes of colloids	**Bunn *et al*, 2003[38] (searches completed 2000)**	**P:** Patients requiring volume replacement or maintenance of colloid osmotic pressure **I:** Any colloid **C:** Any different class of colloid **O:** Mortality	There was no statistically significant difference between albumin/PPF versus gelatin (1 study), modified gelatin versus hydroxyethyl starch (9 studies) or albumin/PPF versus hydroxyethyl starch (11 studies)	This appears to a be a well conducted review; it is unlikely that any relevant studies were missed; no conclusions can be drawn regarding the effectiveness of different colloids in trauma patients as all meta-analyses contained a mixture of patient types; in addition there were differences between studies in clinical parameters such as fluid administration protocols, additional interventions and case-mix
	Overall conclusion: no evidence of the effectiveness of a particular colloid over another in trauma patients			

P: population, I: intervention, C: comparator, O: outcome

Conclusion: choice of fluids

Systematic reviews comparing all types of crystalloids and colloids

The four systematic reviews showed either no difference between crystalloids and colloids with respect to mortality, or a trend towards crystalloids being slightly more effective (although not significantly so). Two of the reviews were methodologically poor or had poor reporting of the methodology (Velanovich, 1989[41] and Bisonni *et al*, 1991[36]), whilst the other two appeared to be well-conducted (Schierhout & Roberts, 1998[40] and Alderson *et al*, 2003[34]). Three reviews compared fluid use in trauma population sub-groups (Velanovich, 1989[41], Bisonni *et al*, 1991[36] and Schierhout & Roberts, 1998[40]), one study compared fluids according to fluid sub-groups and combined patients with trauma, burns, sepsis or undergoing surgery (Alderson *et al*, 2003[34]). All four reviews included clinically heterogeneous studies in terms of different types of colloids and crystalloids administered, case mix, additional interventions received, resuscitation protocols, amounts of fluid administered etc. No conclusions can be drawn from these reviews regarding the effectiveness of a particular type of colloid or crystalloid for a given trauma patient.

Systematic review comparing isotonic crystalloids versus any colloid (Choi et al, 1999[39])

There was a significant difference in terms of mortality between crystalloids and colloids, favouring crystalloids, in the trauma-sub-group. The review appeared to be well-conducted, but again included clinically heterogeneous studies in terms of different types of colloids and crystalloids administered, case mix, additional interventions received, resuscitation protocols, amounts of fluid administered etc. No conclusions can be drawn from these reviews regarding the effectiveness of a particular type of colloid or crystalloid for a given trauma patient.

Systematic reviews on albumin/PPF versus no albumin or crystalloid

There was a trend towards the control (no albumin or crystalloid) being more effective in terms of preventing mortality (Alderson *et al*, 2003[35] and Wilkes & Navickis[43]). It should be noted, however, that the majority of patients included in both reviews within the trauma/surgery/hypovolaemia sub-groups were patients undergoing surgery. In addition, those studies with trauma populations were clinically heterogeneous (as listed above). Both reviews appeared to be well conducted, however, there is no evidence to support the use of albumin in trauma patients.

Systematic review on isotonic versus hypertonic crystalloid (HS) or hypertonic crystalloid with dextran (HSD) (Wade et al, 1997[42])

There were no statistically significant differences in terms of mortality between isotonic saline and hypertonic saline, with or without dextran. This appears to have been a well-conducted review and there was less clinical heterogeneity between studies in this review compared to the others listed here. Some clinical heterogeneity however remains (for example relating to case mix, timing of intervention) and the effect of this is uncertain. No conclusions can be drawn regarding the effectiveness of a specific fluid type, although there was a trend towards hypertonic saline with dextran being more beneficial.

Systematic review on isotonic versus hypertonic crystalloid (Bunn et al, 2003[37])

There was no statistically significant difference in terms of mortality between isotonic and hypertonic crystalloid (the trend was towards hypertonic crystalloid being more beneficial). Again, although this appears to be a well-conducted review, there was clinical heterogeneity

between studies and conclusions regarding the effectiveness in a given trauma patient cannot be drawn.

Systematic review of different classes of colloids (Bunn et al, 2003[38])
There were no statistically significant differences between different classes of colloids regarding mortality. This appears to have been a well-conducted review, however, as different types of patients were combined in the meta-analyses (patients with trauma, sepsis, hypovolaemia, undergoing surgery or other), and there was additional clinical heterogeneity between studies, it is not possible to draw conclusions regarding a particular type of colloid in a given trauma patient.

Summary
The majority of systematic reviews were well conducted and it is unlikely that any relevant studies were missed. No attempt was made by the authors of this report to identify whether there was any overlap between the studies in terms of included trials. All included RCTs only, which are most likely to give unbiased evidence. The reviews generally had broad inclusion criteria (critically ill patients) and the included studies for each review differ in many factors, including: timing of fluid administration, volume and specific type of fluid, variable weight colloids where colloids were a comparator, resuscitation protocols (both pre-hospital and in hospital), case mix, patient characteristics and additional interventions received. In some studies, patients with burns, sepsis or undergoing surgery are also included. These patients are likely to differ in their physiological response from trauma patients who are actively bleeding. It is uncertain whether the included studies reflect current practice in the UK. A statement regarding the suitability of a particular fluid for a particular type of trauma patient is not possible based on these reviews. Caution should be exercised when interpreting the trend towards greater effectiveness of crystalloids generally compared to colloids generally, as effects of individual crystalloids or colloids or crystalloid-colloid mixes might be obscured (for example, the study by Wade *et al* (1997)[42] found a trend towards HSD being slightly more effective compared to isotonic saline than hypertonic saline alone, although the results were not statistically significant).

None of the reviews address the question of whether there is a difference in effectiveness between early administration of fluids compared to delayed administration, between administration of different volumes of the same fluid or a difference between hypotensive versus aggressive fluid resuscitation. Fluid management protocols may also include the use of combinations of fluids at different times.

3.2.4 Summary of all evidence

Table 10 summarises all available evidence surrounding the issues of volume or delay of fluid cannulation and time delay and fluid choice.

Table 10 Summarys of all evidence

Issue/guideline	Study	Design	Conclusion of Assessment	Summary
Fluid resuscitation policy • Boluses of 250 ml fluid may be titrated against the presence or absence of a radial pulse (caveats; penetrating torso injury, head injury, infants)	**Bickell *et al*, 1994[26]**	**RCT**	**Suggestive of IV fluids being harmful in trauma patients with penetrating injury**	Insufficient evidence to recommend a particular fluid management regime in terms of early or delayed fluids for a given trauma patient; insufficient evidence to conclude that pre-hospital IV fluids are harmful , but no evidence to suggest benefit
	Turner et al, 2000[27]	*RCT*	**Insufficient evidence of either harm or benefit of IV fluids**	
	Dutton et al, 2002[28]	*RCT*	**Insufficient evidence to suggest benefit or harm of resuscitation to different blood pressures**	
	Dunham et al, 1991[29]	*RCT*	**Insufficient evidence of harm or benefit of rapid infusion (trend towards rapid infusion being harmful, at least in the short term)**	
	Sampalis *et al*,1997 [44]	Observational study	**Suggestive of IV fluids being harmful in conjunction with a long time delay, although study subject to confounding making interpretation impossible; no evidence to suggest that IV fluids are beneficial**	
	Kwan et al, 2003[30]	*SR*	**No evidence to support the use of IV fluids in uncontrolled haemorrhage**	
	Mapstone et al, in press[31]	*SR (animals)*	**No conclusions regarding fluid use in humans possible**	

The evidence above is coded using font types as follows: **BOLD: evidence identified for assessment report and cited in Consensus Statement;** *ITALICS: evidence only identified in this assessment report;* NORMAL: evidence only cited in Consensus Statement; the evidence cited in the JRCALC guidelines has not been highlighted separately as it is contained within the Consensus Statement evidence

Issue/guideline	Study	Design	Conclusion of Assessment	Summary
Cannulation and time delay • Cannulation should take place en route, where possible • Only two attempts at cannulation should be made • Transfer should not be delayed by attempts to obtain intravenous access • Entrapped patients require cannulation at the scene	**Nicholl *et al* 1998[16]**	**Observational study**	**The study is too biased in patient selection criteria to conclude that crews without ALS training are harmful or beneficial to trauma patients**	Insufficient evidence to conclude that paramedic interventions given at the scene are beneficial over and above the potential harm caused by delaying definitive treatment; there is some evidence to suggest that delaying definitive treatment produces an adverse outcome
	Demetriades *et al*, 1996[50]	Observational study	**Suggestive of non-ALS transport being beneficial, however confounding makes results difficult to interpret**	
	Jacobs *et al*, 1984[5]	Observational study	**Results of the study are uninterpretable; no evidence to suggest that ALS is beneficial or harmful**	
	Pepe *et al*,1987 [51]	Observational study	**Study likely to have been too underpowered to be able to show a relationship, or the lack of one, between pre-hospital time and death rates**	
	Liberman et al, 2000[32]	*Systematic review*	**No evidence to suggest ALS is effective; trend towards BLS being more effective, however confounding in individual studies contributing to review makes the results impossible to interpret**	
	Sethi et al, 2003[33]	*Systematic review*	**See Nicholl *et al* 1998[16] (only included study in this review)**	

The evidence above is coded using font types as follows: **BOLD: evidence identified for assessment report and cited in Consensus Statement;** *ITALICS: evidence only identified in this assessment report;* NORMAL: evidence only cited in Consensus Statement; the evidence cited in the JRCALC guidelines has not been highlighted separately as it is contained within the Consensus Statement evidence

Issue/guideline	Study	Design	Conclusion of Assessment	Summary
Fluid choice • Normal saline is recommended as a suitable fluid for administration to trauma patients	*Velanovich, 1988*[41]	*Systematic review*	**No evidence of benefit of a particular crystalloid or colloid in trauma patients**	Insufficient evidence to recommend a particular fluid for a given trauma patient
	Bisonni et al, 1991[36]	*Systematic review*	**No evidence of benefit of a particular crystalloid or colloid in trauma patients**	
	Schierhout & Roberts, 1998[40]	**Systematic review**	**No evidence of benefit of a particular crystalloid or colloid in trauma patients (potential trend towards crystalloid being more effective)**	
	Alderson *et al*, 2003[34]	**Systematic review**	**No evidence of benefit of a particular crystalloid or colloid in trauma patients (potential trend towards crystalloid being more effective)**	
	Choi *et al*, 1999[39]	**Systematic review**	**No evidence of benefit of a particular crystalloid or colloid in trauma patients**	
	Alderson et al, 2003[35]	*Systematic review*	**No evidence to support the use of albumin over another fluid in trauma patients**	
	Wilkes & Navickis, 2001[43]	*Systematic review*	**No evidence to support the use of albumin over another fluid in trauma patients**	
	Wade et al, 1997[42]	*Systematic review*	**No evidence of benefit of a HS or HSD over isotonic crystalloid in trauma patients (potential trend towards HSD being more effective)**	
	Bunn et al, 2003[37]	*Systematic review*	**No evidence of benefit of isotonic or hypertonic crystalloid in trauma patients (potential trend towards hypertonic crystalloid being more effective)**	
	Bunn *et al*, 2003[38]	**Systematic review**	**No evidence of the effectiveness of a particular colloid over another in trauma patients**	

The evidence above is coded using font types as follows: **BOLD: evidence identified for assessment report and cited in Consensus Statement;** *ITALICS: evidence only identified in this assessment report;* NORMAL: evidence only cited in Consensus Statement; the evidence cited in the JRCALC guidelines has not been highlighted separately as it is contained within the Consensus Statement evidence

4. ECONOMIC EVALUATION

4.1 Existing studies identified

We found three economic evaluations of IV fluid use by paramedics in the literature relevant to the UK context[16,27,52] and there was one cost-effectiveness analysis of the use of a hypertonic solution (HyperHAES®) in the industry submission to NICE from Fresenius Kabi. Full details of the economic search strategy are listed in Appendix 3.

Further enquiry revealed that one of the UK economic evaluations[52] had been withdrawn at the request of the author because of methodological flaws (personal communication Knapp). Therefore this report is not considered further. The other three evaluations are reported below.

4.1.1 Turner *et al* 2000[27]

Type of economic evaluation: the authors set out to complete an incremental cost/benefit analysis based on the findings of their RCT and present a cost analysis.

Perspective: societal

Time horizon: "long-term costs". These are not further specified but the trial had six month follow up, although the economic evaluation does not provide patient costs covering all aspects of care in the six months following the incidents.)

Options compared: the two protocols from the Turner RCT (viz. on scene administration of IV fluids vs fluids withheld until arrival at hospital).

Resources and costs:
Resources that would differ between protocols were identified, measured and costed. The resources identified have face validity and were measured and valued using acceptable sources of information. However the individual component costs are not all stated. In-patient costs were imputed from length and location (ward vs ICU) of stay observed in the trial. For IV fluid use and ambulance call-out time the figures were also taken from the trial. Although data were taken from a randomised trial, they were adjusted statistically for differences between the two groups for important prognostic factors (age, injury severity, patient consciousness at the scene.)

Sensitivity analyses: one-way sensitivity analysis was undertaken varying the three largest components of cost by plus or minus two standard deviations from the mean value of national ambulance and regional hospital costs. This produced an excess cost for IV fluids on scene of between £19-£56/patient.

Findings: The pre-hospital mean cost of IV fluids on scene was £419 and delayed fluids was £416 (p=0.89), and the mean total costs were £2706 and £2678 respectively (p=0.52). A *"more complex analysis… was not thought necessary given the lack of clinical differences between the two trial groups".*

Conclusion: There were no statistically significant differences in costs nor benefits between the two strategies.

4.1.2 Nicholl *et al,* 1998[16]

Type of economic evaluation: the authors present a cost-consequences analysis (the reason given is that, because of the uncertainty about which alternative treatment strategy is superior, relative cost-effectiveness cannot be assessed).

Perspective: NHS perspective.

Time horizon: Not stated but presumably the six months post-incident period covered by the observational study.

Options compared: Paramedics vs non-paramedic pre-hospital care for trauma patients.

Resources and costs: There was a bottom-up costing study that collected resource-use data at all stages of treatment for patients from three different ambulance services in England. Resources include both ambulance service training costs (derived using a bottom-up approach) and service costs (estimated using a top-down approach) and included all relevant elements including treatment costs during and after hospitalisation. The base-case analysis assumed there would be some reduction in training and salary costs because of a reduced level of skills being taught to future paramedics or the full range of skills being taught to a reduced number of paramedics. However they recognised that even a negative result for the benefits of paramedic intervention might simply lead to a change in protocol and there would be no changes in the incremental costs of training and employing paramedics and this is considered in the sensitivity analysis.

In-patient ICU and ward stays were costed by length of stay using regional average unit costs. Out-patient, GP contacts and nurse visits were also included.

Full details are given about the resources costed, the measures used and the sources of data. Unfortunately the individual values are not given, only the composite costs of ALS and BLS and thus it is difficult to assess their validity or utilise them in different analyses.

Findings: All costs are in given 1996/7 prices. Table 11 below gives the average cost of ALS and BLS calls.

Table 11 Average cost of calls in three ambulance services in England (1996/7 prices)

Ambulance Service	Catchment population (millions)	Persons/ k (m^2)	No. of stations	No of A&E ambulances	Average cost of ALS call out (£)	Average cost pf BLS call out (£)	Unit cost of ALS crew (£/min)	Unit cost of BLS crew (£/min)
Area 1	2.7	2505	35	81	63.67	59.33	1.97	1.95
Area 2	1.4	250	14	32	97.19	97.77	2.91	2.90
Area 3	2.1	636	29	99	82.39	76.96	2.45	2.44

Adapted from Nicholl *et al*[16]

As might have been surmised the cost increases as the density of the population decreases because of the increasing proportion of the cost being due to travel times rather than on-scene

activity. The difference between areas has face validity. By comparing the unit/cost of ALS and BLS crews per minute one can see that there is virtually no difference between them in each area. The main difference in cost, therefore, being due to increased time spent on the call. It is not possible to distinguish whether this is due to inappropriate delay or because ALS crews tend to get sent to more complex and serious injuries and accidents, which necessarily take longer. The analysis uses the measured differences in patient characteristics and treatment utilisation. Analysis of variance was undertaken in order to estimate the independent effect of the crew type on resource use and costs. The authors note that "the overall fit of the model was low". The analysis suggests that the ambulance costs are around £4 greater for when there is a paramedic in the crew than for technician-only crews. The mean total cost of all treatment is £2231 for patients who were attended by a paramedic-crewed ambulance and £2209 by those attended by a technician crew. This difference of £22 (1%) was not statistically significant (p=0.814). Moreover, this difference could be confounded by the differences between the type of case attended (mortality 6.2% for paramedics and 4.3% for technician-only crews) and the biases of the observational study design (see section 3.2.2.2). The sensitivity analysis showed that the analysis was insensitive to changes in assumptions such and problems from missing data.

The economic evaluation is presented simply as a cost-consequence analysis as the authors felt it was not possible to know how the mortality risk and morbidity benefits they had measured trade-off against each other. *"Without knowing whether paramedic attendance is preferable to EMT attendance, we cannot say which policy is superior in terms of overall outcomes".*

Conclusion: There is no significant difference in the cost of paramedic versus technician crews for trauma. The relative cost-effectiveness is not known.

4.1.3 Fresenius Kabi 2003[53]

Type of economic evaluation: Claims to be a cost-effectiveness analysis but no costs given

Perspective: Not stated, appears to be NHS

Time horizon: Not stated

Options compared: One option is the use of HyperHAES® the other appears to be no IV fluids (Fresenius Kabi's assumption 6) rather than current standard treatment.

Resources and costs: The report is based on many (10) assumptions about hospital bed utilisation by trauma patients, most of which had no referenced source. There were no costs put on hospital utilisation and the outcome is reported in bed days saved

Effectiveness data: The major weakness of this paper is that it is based on benefits deduced from animal studies.[54,55] The authors explain *"As hypertonic saline with a colloid in animal studies demonstrated that organ perfusion is resumed within 5 minutes, the assumption is that this may lead to a reduced number of patient bed days due to the avoidance of Multi Organ Failure."* How the specific estimate is made from animal models to humans is not stated.

Findings: The authors state in the economic evaluation that if HyperHAES® were adopted the average length of patient stay in days would reduce, therefore an additional 44,406 patients could be treated in ITUs over a five-year period. In the executive summary this is inappropriately reported as an *annual* saving of 44,406 bed days

Conclusion: This is not a full economic evaluation. The evidence in humans for the use of this fluid in pre-hospital trauma is not yet established. This evaluation gives no useful information to inform the cost-effectiveness discussion of IV fluid use in the pre-hospital situation.

4.1.4 Further economic evaluation

We did not undertaken an independent economic evaluation for this report, for the following reasons:

1. Some costs are trivial

   - The giving sets and fluids currently used are extremely cheap (see Table 2 and Table 3), and there is no evidence to suggest that the routine use of more expensive fluids might be justified (indeed colloids are being withdrawn under JRCALC).

   - The Nicholls evaluation and the PSSRU data show that training costs for paramedics (which only lasts an additional eight weeks in the UK) are a negligible component of overall costs.

   - A policy of not using fluids for certain categories of patients would not obviate the need for ambulances to carry fluids (they are needed, for example in patients with head injury or diabetic ketoacidosis), nor personnel with the skills required to administer them. In particular, the desirability of early cannulation and the need for other advanced life support skills on board, suggests that the extent to which fluids are administered pre-hospital will have little effect on training and staff costs.

   - Training costs are negligible.

   - Most of the ambulance service time is spent waiting for calls or travelling. Therefore even a substantial increase in time on scene would not increase the total costs of the service as it would not necessitate and investment in more equipment or personnel except at the margins. 'Cost per minute' calculations, based on the total costs of running the service divided by the total number of minutes spent on all calls, are not useful for deciding between options. The main effect of longer call out times suggested would simply be to reduce the overall cost/minute and not the total cost to the service. Thus although the use of IV fluids may increase time on scene, and the nominal cost of the call-out, there is no true cost impact on the ambulance service.

2. The length of stay in hospital is a substantial cost. Since what evidence there is is suggestive that this is reduced in a cautious resuscitation policy (Bickell found a statistically significant three day longer stay for patients who were immediately resuscitated), the costs and consequences move in the same direction and would dominate.

3. A potentially substantial cost that could alter the policy decision is the cost of care for patients who survive with organ damage or other serious complications of trauma. However, we know neither the direction nor size of any such effect. Despite the trend noted in Bickell for more post-operative complications in the immediate resuscitation group, including acute renal failure (4% vs 1% p=0.11), there is insufficient evidence to reliably quantify effects. We have no accurate estimate of life years gained nor costs (which would be heavily influenced by the numbers surviving in the longer term with chronic health problems).

4. The absolute number of patients affected is extremely small.

4.2 Conclusion re cost-effectiveness:

There are unlikely to be cost savings by converting to EMT-only ambulance crews or changing resuscitation protocols for current crews.

The important considerations for making an appropriate policy decision about IV fluid resuscitation are not potential cost savings but rather issues of clinical effectiveness such as preventing on-scene delay (thereby reducing adverse outcomes), establishing what, if any, should be the indications for IV fluid use and in ensuring that the findings are implemented in practice not just in guidelines. (This might require more resources to fund an adequate national audit and educational initiatives to ensure that the less aggressive resuscitation policies recently recommended are implemented.)

5. DISCUSSION

5.1 Main results

A health technology assessment on the benefits of paramedic skills in pre-hospital trauma care in England was published in 1998.[21] The report concluded that protocols used by paramedics in England increased the mortality from serious trauma involving bleeding injuries but may have led to better outcomes for survivors. The most likely factors identified to account for the excess mortality were delays on scene and inappropriate pre-hospital fluid infusion.

Our systematic review has revealed that the evidence base to inform this topic has not altered substantially since the publication this report. This is also consistent with the findings of the Cochrane systematic review (Kwan *et al*, 2003[30]). The authors of the 1998 HTA report anticipated that an NHS-funded trial, in progress at the time, comparing two protocols for fluid resuscitation in blunt trauma might provide useful evidence. However, due mainly to the poor implementation of the randomised protocols by the ambulance crews and the poor selection of patients by the trial design, the study was underpowered and the results were not informative.

Of the four RCTs concerning fluid delay or different fluid volumes, three were methodologically flawed or unsuccessful in their implementation. Only one study (Bickell *et al*, 1994[26]) allows some tentative conclusions to be drawn and suggests that there is some harm from giving pre-hospital IV fluids. This study however relates to patients with penetrating injury, whereas the trauma population in the UK has mainly blunt injuries.

Observational studies appear to suggest the same trend, however, these studies are by their nature confounded, with more severely injured patients (who are more likely to die) generally receiving additional interventions such as IV fluids and being subject to longer time delays. Although known confounders can be adjusted for, unknown confounders invariably bias observational studies making it difficult to interpret the findings.

Since the 1998 HTA report, updated JRCALC guidelines and a Consensus Statement on pre-hospital treatment of trauma patients have been published. Both of these emphasise the need to prevent delay to definitive treatment and mark a shift towards a more cautious (hypotensive) fluid resuscitation policy. Both documents make reference to the fact that the evidence suggests fluids may do more harm than good in patients with penetrating injuries. The Consensus Statement gives differing advice for fluid resuscitation in penetrating torso trauma than for blunt injury

> *"Fluid should not be administered to trauma victims prior to haemorrhage control if a radial pulse can be felt. Judicious aliquots of 250 mls should be titrated for other patients. If the radial pulse returns, fluid resuscitation can be suspended for the present and the situation monitored. In penetrating torso trauma the presence of a central pulse should be considered adequate."*

We found pathophysiological arguments for supporting fluid resuscitation (e.g. the need to prevent hypoperfusion) and pathophysiological arguments for withholding fluid resuscitation (e.g. risk of mechanical displacement of clots and interference with clotting mechanisms). However we did not find compelling pathophysiological explanations to suggest that these arguments would apply differentially to blunt injuries and penetrating injuries.[56,57] Indeed the Consensus Statement notes that:

> *" there is little available data from human studies regarding whether blunt trauma differs significantly from penetrating trauma in its behaviour."*

There are some specific cases such as pericardial tamponade (a blunt injury where there is a need to sustain BP until the tamponade is relieved) where there could be good reasons to resuscitate but these do not appear to apply to the majority of blunt trauma injuries and would probably be outside the skills of most paramedics to diagnose in the field.

5.2 Assumptions, limitations and uncertainties

So why do guidelines offer differing advice for blunt and penetrating injuries? One reason for the discrepancy between the penetrating trauma advice and the blunt trauma advice could lie in the historical evolution of our understanding of this matter. Thus the dominant view, rooted in the early controlled-haemorrhage animal model studies, was that aggressive fluid replacement was a "good thing". When empirical evidence from observational studies and the Bickell trial demonstrated that aggressive fluid resuscitation probably did more harm than good, the weight of this evidence was only sufficient to overturn people's prior beliefs about the benefits of fluid resuscitation in penetrating injury and could only shift their prior beliefs about resuscitation in blunt trauma to the more conservative position of permissive hypotensive resuscitation. We have found no pathophysiological reasons or empirical evidence that would suggest to us that the intervention is likely to be more beneficial or less harmful in blunt than penetrating injury. Therefore, although there is no reliable evidence on

the outcomes of fluid resuscitation in blunt trauma, we believe that the onus of proof should be on the intervention and not *vice versa*.

When considering the question of whether there may be differences in sub-groups of patients, such as blunt versus penetrating trauma, there are substantial methodological problems that must be borne in mind. Sub-group analysis aimed at identifying groups of patients which might respond differently to treatment has relatively low power and a high probability of false positive findings. Observational studies are not reliable sources of data for such investigations and cannot be used to reliably test hypotheses regarding sub-group outcomes. The existing RCT data is limited in both quantity and quality and so it is unlikely that reliable results could be obtained from the existing data.

Unfortunately, even with the availability of more high quality data, it might not be possible to define clinically relevant sub-groups for whom different resuscitation policies are appropriate. To be of clinical rather than purely scientific interest, sub-groups must be accurately identifiable solely through information available on-scene, based on judgements made by technicians and paramedics at that time. Ascertaining such information should not incur any additional time on-scene.

The information available on-scene is relatively limited, and the condition of the patient may not be particularly accurately assessed under conditions in the field. Nearly all studies reviewed in this report have used reduction in blood pressure as one of the main inclusion criteria and yet hypotension does not necessarily lead to hypoperfusion and shock. Some studies have looked at the ability of emergency crews to diagnose haemorrhagic shock using the limited information available to them.[58,59] Whilst blood pressure is the single most useful indicator, sensitivity and specificity are low, and are strongly influenced by the presence or absence of head injury which may interfere with normal haemostatic mechanisms.

It may be the case that, were it possible to accurately identify those patients in shock or impending shock, the net benefits of fluid replacement in this group could exceed the harms. Using less reliable indicators, such as blood pressure, may not be helpful. For example, although it could be argued that the use of a very low blood pressure threshold for resuscitation might help to restrict the use of fluids to those at greatest risk of hypoperfusion and subsequent organ damage, the low threshold would also identify patients with the most severe bleeds, who may be the most likely to be actively harmed by fluids disrupting clotting mechanisms. What would be required is a reliable field diagnosis of shock (some are currently under investigation for military purposes (Bickell personal communication)). Given the difficulty of accurately diagnosing haemorrhagic shock at the scene, it seems that unlikely that without new tools diagnosis could be further refined to reliably identify those patients for whom the risks of fluid resuscitation might outweigh the benefits, and vice versa.

This technology assessment report raises several very important issues:

1. Practice still appears to be lagging behind current knowledge and recommendations. Although the degree to which this is the case is hard to quantify because of the lack of available data about practice.
2. Through conversations we have observed that widely differing beliefs about best practice are held by the paramedical community. Worryingly these beliefs are often very firmly held despite the weakness of the clinical evidence base. This suggests

that future trials, like past trials, may prove difficult to conduct as people may be reluctant to follow protocol when it goes against their convictions about what is in the best interest of the patient.

3. There are almost certainly avoidable on-scene delays
4. Despite the collection of an agreed and comprehensive minimum data set, this information is not readily available to practitioners nor decision makers.

Although there is a clear need to improve our knowledge base in this area, it is also important to ensure that current practice is consistent with current best evidence. Our conversations with paramedics and related staff and the limited recent empirical evidence that is available suggest that frequently this is not the case and that paramedical crews are still working within an outdated paradigm with consequent delays in the time to definitive treatment by on scene interventions and assessment.

5.3 Future research

Randomised controlled trials

RCTs are extremely difficult to conduct in this area. In particular, the necessity of avoiding pre-hospital delay makes usual consent and randomisation procedures impossible. The approaches adopted by trials conducted in a pre-hospital setting have effectively been to pre-randomise all patients using a cluster design, by randomising either paramedics or days to a particular resuscitation protocol. This approach necessitates retrospective selection of patients as the vast majority attended will not be suffering from hypovolaemia due to blunt or penetrating trauma. Trialists must therefore take great care in designing studies to avoid bias in the retrospective application of eligibility criteria and ensure that the results are interpretable:

- Eligibility criteria are required which can be applied independent of outcomes and which are assessable based on information available at the time of attendance by paramedics (even if the actual decision to include/exclude is not made at this time)
- Decisions to include/exclude should be made by an independent panel, blinded to patient outcomes, and based only on information recorded by paramedics and technicians at the scene
- Eligibility criteria should, as far as possible, define the patient population which would be considered for resuscitation in current practice and exclude the majority of other cases
- It may be the case that the development of rapid tests for shock suitable for use in the field may make trials more feasible by permitting trialists to use eligibility criteria that are more appropriate and specific
- Power calculations should be performed taking into account the likely extent of dilution by inclusion of some patient groups who could not be excluded by this mechanism
- Surrogate outcomes should not be used as a substitute for mortality and longer term morbidity measures
- Follow-up should be long enough to pick up late deaths (TARN recommend a follow-up period of 30 days for trauma deaths, although it should be noted that 6% of deaths occur in the period up to 93 days)[23]; a period of 6 months may be appropriate for assessing long-term effects on morbidity
- Sub-group analysis of data from future trials, should proceed cautiously and aim to test clear pre-defined hypotheses concerning the outcomes for different patient groups.

New fluids
New fluids should not be adopted for use without being shown to be superior to alternative treatments in high quality clinical trials. These trials should not be solely against standard fluids but, in the light of the lack of evidence for the benefits of fluids in certain types of trauma, should include an arm with a very cautious fluid resuscitation protocol.

Observational data
Routinely collected data for ambulance call-outs has the potential to assist researchers in this area considerably. The Ambulance Service Association launched a recommended minimum data set in 1999 to encourage consistency, completeness and timeliness of recording of information to assist audit and research (see Appendix 7, ASA/JRCALC Minimum data set).

A survey conducted in 2000[21] to assess adherence to this found several shortcomings and led to the following recommendations:

- "The ASA NCEP to create a register of current patient report forms in use by UK ambulance services.
- "The ASA NCEP to create a register of other data collection methods in use by ambulance services, including arrangements for data collection required as part of the National Service Framework for Coronary Heart Disease (CHD NSF).
- "All ambulance services to adopt standard data collection procedures for the CHD NSF through the use of the ASA/JRCALC clinical audit database for pre-hospital cardiac care.
- "All ambulance services to share best practice in patient report form design and data collection, including the standardisation of codes used.
- "All ambulance services to revise the design of their patient report form in terms of content in light of NSF's and JRCALC guidelines.
- "All ambulance services to ensure data is collected for every patient episode.
- "The following principles should be adopted when redesigning patient report forms:
  a) Move towards real time data collection
  b) Improve the efficiency and accuracy of data collected from the PRF
  c) Reduce 'waste' both on the form and in the processes of collection and analysis i.e. remove anything that does not add value or takes value away
  d) Ensure the patient report form meets the needs of patient data requirements e.g. NSF's and national guidelines
  e) Reduce or eliminate the variation in the quality of data collected, both between individual patient report forms and between ambulance services"

Implementing these recommendations successfully would provide a valuable tool for both audit and research in this area, and is critical for the monitoring of guideline use by different ambulance services. It is important that the data *are* routinely analysed and reported and made accessible to researchers for additional analysis.

6. CONCLUSIONS

We found no evidence to suggest that pre-hospital IV fluid resuscitation is beneficial. Indeed there is some evidence, particularly from the study by Bickell *et al* (1994) and some observational studies, that it may be harmful and that that patients do comparatively well when fluids are withheld. However, this evidence is not conclusive (particularly for blunt

trauma) and thus there is not sufficient evidence to contradict the Consensus Statement guidelines which recommend hypotensive resuscitation.

As the Consensus Statement, and to a lesser extent the JRCALC guidelines, represent a more cautious approach to fluid management than previously advocated, the implementation of these guidelines should be supported. Currently it is difficult to assess the extent to which these new guidelines represent current practice in the UK as ambulance audit data is often absent or poorly recorded. Anecdotal reports to us suggest that they may not be being adhered to.

Further research would be needed to establish whether hypotensive (i.e. cautious) resuscitation is more effective than delayed or no fluid replacement or whether resuscitation in blunt trauma should be more aggressive than in penetrating injury, as implied by current guidelines.

Appendix 1 Consensus Statement

MATTER FOR DEBATE
Fluid Resuscitation in Pre-Hospital Trauma Care: a Consensus View
I. GREAVES, K.M. PORTER and M.P. REVELL

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Groups represented: Faculty of Pre-hospital Care & Faculty of Accident & Emergency Medicine, Royal College of Surgeons of Edinburgh, The United Kingdom Military Defence Forces, Ambulance Service Association with Paramedics representatives, British Association for Immediate Care (BASICS), London Helicopter Emergency Medical Service (HEMS) and Researchers with an interest in Pre-hospital Care

Fluid administration for trauma in the pre-hospital environment is a challenging and controversial area. The available evidence does not clearly support any single approach. Nevertheless, some provisional conclusions may be drawn. It was with this intention that the Faculty of Pre-Hospital Care (RCSEd) arranged to meet in August 2000 in an attempt to reach a working consensus. The following guidelines are the result of those discussions. It is intended that they will be modified as future research brings clarity to the area. When treating trauma victims in the pre-hospital arena cannulation should take place en route, where possible. Only two attempts at cannulation should be made. Transfer should not be delayed by attempts to obtain intravenous access. Entrapped patients require cannulation at the scene. Normal saline may be titrated in boluses of 250 ml against the presence or absence o f a radial pulse (caveats; penetrating torso injury, head injury, infants).

Keywords: fluid resuscitation, trauma care, clinical practice

INTRODUCTION
Evidence-based medicine describes clinical practice in which patient care and therapeutic decisions are supported by information gained from a careful consideration of the available worldwide research literature. Ideally, unequivocal clinical conclusions should be drawn based on the results of carefully conducted studies. Unfortunately, even at the beginning of the twenty-first century, in many areas this evidence is patchy or contradictory. Furthermore, a number of the most fundamental questions confronting present day clinicians may never be answered by suitably conducted studies. Initial evidence might suggest, for example, that a particular treatment offers a small survival advantage compared with another, but the number of recruits required to ensure a meaningful trial may render it impractical in terms of logistics and cost. In addition, an increasingly complex ethical framework makes it likely that many definitive clinical studies would not gain ethical approval.

In the meantime, practitioners in all disciplines have to try to base their clinical decisions on whatever sound evidence is available. Most clinicians also find it helpful to discuss experiences and ideas. Although such exchanges tend to be anecdotal, they often fill the gaps in our present scientific knowledge, allowing decisions to be made regarding patient care on the basis of shared experience, where firm evidence is inconclusive or absent.

It is with the aim of reconciling clinical experience and current evidence in the pre-hospital trauma setting that the following article has been prepared. Evidence from the scientific literature is cited where possible. The remainder is a consensus reached by experienced trauma personnel from a variety of backgrounds (Pre-hospital Fluid Resuscitation in Trauma: a consensus meeting. Faculty of Pre-hospital Care, University Hospital Birmingham, August 2000). The concept of value being added to raw data through the input of acknowledged authorities is a well-established process in evidence-based medicine.[1]

These guidelines provide one simple strategy applied to the use of fluids for trauma patients in the pre-hospital setting. Three main areas have been addressed -cannulation, the choice of fluid and the quantity of fluid given.

It is intended that these issues should continue to be debated and, where ideas and concepts are put forward, it is expected that they will evolve or change as experience and evidence accumulate.

CANNULATION

Issues

Early venous access in trauma patients has traditionally been regarded as of great importance.[2,3] It allows administration of fluids, where necessary, or other drugs such as anaesthetic, analgesic and resuscitation agents.[4] Placement of a venous line is likely to be technically easier in the early stages of shock than when hypovolaemia has progressed and compensatory mechanisms have resulted in peripheral vasoconstriction. As a consequence, paramedics have been encouraged to use such skills in trauma.

While early successful cannulation will save time when the patient arrives in hospital, it is also clear that repeated unsuccessful attempts or access with a cannula of insufficient gauge will hinder progress at the same stage.[5]

Recently, interventions made by paramedics before the patient arrives in hospital have come under close scrutiny. In a retrospective study, Demetriades et al (1996) found that outcome was worse in a group of 4856 patients brought to hospital by paramedics than in 926 patients brought in by bystanders, relatives and the police.[6] Assuming the results are truly representative, it is has been suggested that poor outcomes relate to detrimental effects of pre-hospital advanced life support (ALS) measures. There is other evidence suggesting ALS methods improve survival, but the aggressive use of fluid, in particular, has been called into question.[7]

Independent of the use of intravenous fluids, however, transfer time to hospital appears to be an important predictor of out-come.[8] Improvements may be possible here. Cannulating ambulance crews appear to spend a longer time on scene and this extra time does appear to be related to the interventions they perform.[9-11] If the administration of fluid pre-hospital is open to question, then this apparent delay in transfer in order to obtain circulatory access should also come under scrutiny.

One way to balance the benefits to be gained by obtaining pre-hospital venous access, with the risk of lengthening transfer times, is to attempt cannulation en route.[12] This approach has both training and Health and Safety implications, but has received strong support.[13,14]

The management of entrapped patients is a special situation.[15] Here again, the focus should be on keeping the time to arrival in hospital as short as possible. The coordinated roles of all the emergency services are critical in keeping delays to a minimum.[16] It is likely that efforts to cannulate in these situations will not extend the time of transfer. In addition, there are usually compelling reasons for obtaining a venous line on scene; principally, the need for analgesia but on occasion, for infusion of specific drugs for resuscitation and fluids.

Consensus View

Cannulation at an early stage is desirable. However, in most situations, priority should be given to transfer of the patient to a centre where definitive care can be provided. The on scene time should not be prolonged by attempts to gain a line. Intravenous access during transit has been employed success-fully and should be considered where appropriate expertise and training are available. A limit of two attempts en route is reasonable.

In cases of entrapment, circulatory access should be gained on scene. This reflects the unique demands of this area of pre-hospital medicine.

CHOICE OF FLUID FOR RESUSCITATION

Issues

This area continues to be one in which, despite an increasing body of evidence, no consensus regarding choice of fluid has been reached. Broadly, the choice of options includes:

• no fluid

• crystalloids (isotonic and hypertonic)
• colloids (mainly gelatins and starch solutions)
• oxygen carrying solutions (blood and blood substitutes)

The decision is a complex one and includes consideration of the factors listed in table 1

early haemodynamic effects
effects on haemostasis
oxygen carriage
distribution and capillary endothelial leak
modulation of inflammatory response
safety
pH buffering
method of elimination
practicality and cost

Table 1: Factors influencing choice of fluids

Early haemodynamic effects: The aim of administering fluids is to restore end-organ perfusion and, therefore, oxygen delivery. An increase in circulating volume will have a tendency to increase cardiac output and blood pressure. The rapidity with which a given fluid will produce its effect will largely be determined by its volume of distribution within the body and how quickly it equilibrates. A sudden increase in blood flow may not be beneficial because it has the potential to precipitate rebleeding from sites where physiological mechanisms have brought about cessation of haemorrhage.

Haemostasis: In general, administration of fluid has a detrimental effect on haemostasis and a tendency to increase bleeding.[17,18] To begin with, primary haemostatic thrombus may be dislodged from a vessel causing rebleeding, as outlined above. Most fluids will cause vasodilatation, at least as a result of reversing hypovolaemia, with similar risks. With the obvious exception of fresh frozen plasma, most will also reduce blood viscosity and dilute clotting factors to the detriment of haemostatic mechanisms.

Direct interference with the clotting cascades is seen with some starches.[19] Finally, hypothermia-induced coagulopathy should be avoided, if possible, and the fluids should be warmed prior to infusion.[20, 21]

pH buffering: Acidosis results from anaerobic metabolism of energy substrate, producing lactic acid, phosphoric acids and unoxidised amino acids. This can have negative ino-tropic effects and predispose to arrhythmias. Manipulating pH per se, with the use of bicarbonate, for example, is not presently advised since it impairs oxygen delivery to the tissues by its effect on the dissociation of oxygen from haemoglobin. Some protein-based fluids, such as albumin and fresh frozen plasma, have pH buffering properties, which may be beneficial.[22]

Oxygen carriage: High flow oxygen is administered routinely to trauma patients.[2] The main thrust of fluid administration is directed towards reversing hypovolaemia. In the early stages, the relative anaemia caused by blood loss is compensated for by the decrease in blood viscosity, which allows improved peripheral oxygen delivery. Anaemia associated with haemorrhage is considered to be secondary in importance to hypovolaemia in the accumulation of oxygen debt. To date, no artificial oxygen carrying solutions have reached widespread use.

Modulation of the inflammatory response and capillary leak: Critically ill patients exhibit increased capillary permeability which can allow molecules such as albumin and water to pass into the interstitium exacerbating oedema and impeding oxygen transfer.[23,24] Molecular size is a major determinant of whether a fluid will remain primarily in the intravascular space or be distributed more widely within the extracellular space. Both low molecular weight synthetic colloids and exogenous albumin solutions leave the circulation to a variable degree.[25,26] Conversely, high molecular weight colloids, which remain in the intravascular space, exert an oncotic effect which can result in cellular dehydration. Accordingly, these should be administered with adequate amounts of water.[27] Evidence suggests that high molecular weight starches may have a secondary direct down-regulatory action on capillary leak via an action on endothelial surface molecules.[28]

Safety: The fluid of choice must be one that can be administered safely in all patient groups. Some starches and haemoglobin solutions have detrimental effects on renal function. Anaphylaxis has been seen with blood products in particular, but also with gelatins. The introduction of viral and prion infections is a risk associated with blood and its derivatives. The possible consequences on a cross-match sample in the later stages of treatment have also been raised with the use of dextran; new dextran preparations are believed not to give rise to these problems.[29]

Practicality and cost: The ideal resuscitation fluid should be cheap, with a long shelf life. It should be easy to store and to warm when required. In the rarest of circumstances, pre-hospital administration of blood is almost never achievable.

Consensus View

Modern perfluourocarbons and haemoglobin-b oxygen carriers are currently still largely experimental.[30,31] Blood (together with human albumin solution and fresh frozen plasma) is costly and difficult to store, having a relatively short shelf life. In addition, issues regarding compatibility and disease transmission make blood and its derivatives unlikely candidates as a permanent solution in the pre-hospital situation.

The debate as to the superiority of crystalloid or colloid continues, several decades after it began.[32,33] Many recent publications advocating specific solutions, emphasize the heterogeneity within both categories of resuscitation fluids.[34,35] Resuscitation fluids should be evaluated on an individual basis and not in terms of generic groupings.

Isotonic crystalloid solutions are cheap, easy to store and warm and have an established safety record when they are used appropriately. They produce a relatively predictable rise in cardiac output and are generally distributed evenly throughout the extracellular space. They do not draw water out of the intravascular space. The use of Ringers solution as the fluid of choice in burns has been documented.[36] It offers some buffering capacity but carries a possible risk of iatrogenically increasing lactic acidosis, when given in large doses or to patients with liver failure. [37] Saline in large quantities may produce a hyperchloraemic acidosis.[38] The case for hypertonic solutions in head injury has not yet been conclusively established in a randomised controlled trial. A meta-analysis by Wade et al (1997) strongly suggests a survival advantage and such a trial is urgently required.[39]

At present, isotonic saline is recommended as the first line fluid in the resuscitation of a hypovolaemic trauma patient.

QUANTITY OF FLUID USED IN RESUSCITATION

Issues

The dilemma that faces medical personnel confronted with a hypovolaemic, trauma patient is essentially the balance between:
• administering fluid and, thereby, risking delay in transfer, rebleeding and increased blood loss, and
• withholding fluid and, thereby, allowing the possibility of organ ischaemia and death from hypovolaemia, prior to arrival in hospital

This quandary is not new. Cannon et al (1918) based on experience in the First World War, considered administration of fluids before the surgical control of bleeding to be dangerous.[40] The same outlook governed thinking on fluid replacement in the Second World War. [41]

There is evidence that in penetrating torso trauma, aggressive use of intravenous fluids is detrimental to outcome.[42] In a randomised controlled trial, patients received either no fluid pre-hospital or immediate fluid resuscitation. Reduced mortality and complications were seen if fluid resuscitation was delayed until surgery. Although methodological criticisms have been raised about the study, it remains extremely influential because it is a rare prospective, randomised study in this area.[43] There are also animal studies that raise similar doubts about the effectiveness or safety of early fluid replacement. [44,45]

The majority of trauma seen in the United Kingdom is blunt trauma. Unfortunately, there is little available data from human studies regarding whether blunt trauma differs significantly from penetrating trauma in its behaviour. In a retrospective case-matched review of severe trauma victims, 217 patients who had on-site fluid replacement fared worse, in terms of mortality, than controls receiving no fluid. [46] Increased pre-hospital times and fluid administration were identified as risk factors, requiring further investigation.

Enthusiasm for aggressive fluid resuscitation during the second half of the twentieth century probably had its roots in early animal haemorrhage experiments conducted by Wiggers and other workers in the 1950's and 1960's. 47 In the classic model used, blood was taken out through a catheter until a set pressure was reached, after which withdrawal ceased. Administration of fluid following this improved outcome. Traverso et al (1986) employed a similar porcine model, but this time a fixed volume was removed. 48,49 The problem with both studies is that haemorrhage had ceased prior to resuscitation and would not recommence due to its controlled nature. In the trauma patient, there are no such guarantees.

More recently, animal experiments have attempted to replicate the possibility of uncontrolled haemorrhage more closely. There are two main groups of experiments; external haemorrhage models (e.g. rat tail amputation) and internal haemorrhage models, where a controlled injury to a great vessel or major abdominal artery produces hypovolaemia. Overall, the external haemorrhage models suggest that bleeding and mortality will increase if fluid is administered prior to haemostasis.[45, 50-52] Some authors, however, found improved survival in resuscitated rats, though Sindlinger et al (1993) noted increased blood loss. 53 Soucy et al (1995) identified anaesthetic agents as an important confounding factor and there are many methodological arguments, which make extrapolation to human trauma difficult. [54,55] Internal haemorrhage experiments on rats and pigs appear to provide clearer evidence that aggressive fluid administration reduces survival.[17, 56-58]

Many of the ways in which fluid may worsen bleeding have been outlined already. Bickell et al (1991) discuss these mechanisms in some detail. [17] They suggest that a major danger in penetrating large vessel injury is that the improvement in haemodynamics, brought about by administration of fluid, will cause primary extraluminal thrombus to be dislodged. Using a porcine aortotomy model, they confirmed that aggressive replacement of blood loss with three times the volume of crystalloid increased haemorrhage and decreased survival.

Attention, therefore, has become focused on resuscitation strategies. Stern et al (1995) bled pigs rapidly through a fem-oral catheter then produced an aortotomy using a steel wire. Animals haemorrhaged down to a pulse pressure of 5 torr. They were then resuscitated to a systolic pressure of 40, 60 or 80 torr. The most bleeding and the highest mortality were seen in the 80 torr group. The 60 torr group were less acidotic than the 40 torr group. Riddez et al (1998) performed a standardised aortotomy in dogs. [59] There were four resuscitation groups; no fluid, 1:1 volume ratio Ringers, 2:1 Ringers and 3:1 Ringers replacement. Aortic blood flow increased with the amount of fluid used. Blood loss also increased. The highest mortality was seen in the no fluid and the 3:1 groups. The authors felt that the deaths in the less aggressive fluid replacement groups were due to shock and

those in the more vigorously resuscitated dogs were due to re-bleeding. Similar findings in rats were noted by other groups.[52,60] These findings appear to suggest that the best strategy is not to withhold fluid altogether, but that a moderate replacement policy is likely to be most successful.

Permissive hypotension describes the approach in which the blood pressure is allowed to remain below the normal levels seen in health, with the aim of maintaining vital organ perfusion without exacerbating haemorrhage. A review of hypotensive resuscitation is provided by Hyde et al (1998). [61]

If hypotensive resuscitation is the best paradigm, the problem will be translating its use practically into the field. One prescription will not be suitable for all trauma victims. It is also vital that in the pre-hospital phase of patient care, strategies are straightforward, reflecting the difficulties of treating trauma victims on scene and in transit, without detailed diagnostic information. One method to minimise the risk of excessive fluid administration is to give small boluses of fluid at a time. The number of these could even be limited unless authorisation was sought by means of a call to a control centre. Boluses of 250ml are easy to administer from 500ml or 1 litre bags.

Protocols can be based around easily available physiological measures. The presence or absence of a radial pulse gives an approximate guide to whether the blood pressure is above or below 80-90 mmHg. Brachial pulse corresponds to about 70-80 mmHg and a central (femoral or carotid) to 60-70 mmHg. [62] Deakin (2000, 2001) has recently criticised these figures. [63-65] It is known that a degree of hypotension in trauma can be tolerated and that this tolerance is linked to physiological compensation mechanisms, especially to haemostasis. Differing limits on the degree of hypotension that should be permitted can be found. [66,67] However, it is likely that subgroups tolerate hypotension differently. The head-injured patient may require a higher pressure in order to maintain cerebral perfusion and reduce secondary brain injury. 68 Patients with penetrating torso trauma probably require lower pressures. The elderly are known to tolerate hypotension badly. However, no evidence has been found, so far, that that these patients should receive qualitatively different treatment from the population at large.

Consensus View

Fluid should not be administered to trauma victims prior to haemorrhage control if a radial pulse can be felt. Judicious aliquots of 250 mls should be titrated for other patients. If the radial pulse returns, fluid resuscitation can be suspended for the present and the situation monitored. In penetrating torso trauma the presence of a central pulse should be considered adequate. In children less than 1 year old, the use of a brachial pulse is more practical as it is easier to feel.

SUMMARY

Fluid administration for trauma in the pre-hospital environment is a challenging and controversial area. There is, as yet no equivocal answer or view, which can be supported by clear, well-documented and reliable evidence. Nevertheless, a careful evaluation of what evidence is available does allow some provisional conclusions to be drawn. We believe that the following represent the best possible current expert consensus on pre-hospital fluids in trauma. As future evidence brings clarity to this area, these guidelines can be modified, and further consensus statements will be issued taking into account such information.

When treating trauma victims in the pre-hospital setting:
- Cannulation should take place en route, where possible
- Only two attempts at cannulation should be made
- Transfer should not be delayed by attempts to obtain intravenous access
- Entrapped patients require cannulation at the scene
- Normal saline is recommended as a suitable fluid for administration to trauma patients
- Boluses of 250 ml fluid may be titrated against the presence or absence of a radial pulse (caveats; penetrating torso injury, head injury, infants)

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Appendix 2 Extracts from JRCALC guidelines

TRAUMA EMERGENCIES (p15)

- **Circulation Fluid Therapy**

  - Current international research has show little evidence to support the use of Pre-Hospital IV infusion routinely in trauma patients. In cases of penetrating chest and abdominal injuries and aortic aneurysm dissection, an actual **decrease in survival** has been associated with pre-hospital fluid administration. This clashes with previously held views that IV infusion was both essential and life saving in trauma. The logic however, is that after severe haemorrhage, blood pressure drops, blood loss slows right down and fragile clots begin to form.

  - If IV fluids are given excessively, these fragile clots will be displaced and re-bleeding occurs. As a rule therefore, **IV infusions should be commenced en route to hospital,** and only sufficient fluid given to maintain a systolic BP of 80-90 mmHg, - equivalent to the return and maintenance of a radial pulse. i.e. if SBP is already 90 mmHg, commence fluid, but at a keep vein open (TKVO) rate, and **keep reassessing.**

  - However, in cases where there is delay in reaching hospital, IV fluid therapy may be of more benefit.

  - The emphasis therefore is on obtaining IV access while making a more considered judgement on the need to commence IV infusion. In cases of penetrating trauma IV access should be obtained en route to hospital but fluids should be withheld unless absolutely necessary.

  - En route to hospital (or in situ if trapped) patients with compromised circulation, or potential circulatory problems as a result of their injuries, **should have 1 or 2 large bore (14 or 16 G)** IV lines sited in large veins in the arms e.g. antecubital fossa.

  - 500ml IV of crystalloid solution should be given, and the effects assessed on the circulatory system, before further fluids are given. The aim is to reduce tachycardia and other features of hypovolaemia, whilst maintaining a **systolic BP of around 80 - 90 mmHg.**

  - In the non-trapped patient, only **one limb** should be used for IV access attempts, and an intact site must be left for hospital IV access (unless two IV lines are required and can be achieved).

  - In minor trauma, IV access is most often NOT indicated unless parenteral analgesia is indicated.

INTRAVENOUS FLUID THERAPY (p1/2)

Introduction

Aims of fluid replacement

To restore tissue perfusion and oxygenation

To correct Hypovolaemia

There are two intravenous fluids commonly used by Ambulance Services for volume replacement. Both are a type of crystalloid solution:

Compound Sodium Lactate – (Hartmanns or Ringers Lactate) in 500 or 1000 ml bags

Sodium Chloride (Physiological Saline) 0.9% – in 500 or 1000 ml bags

Hypertonic saline solutions and large molecule starch compounds are currently being evaluated as possible alternatives. Colloids are no longer recommended in pre-hospital care as they have no proven benefit but a higher cost and higher risk of adverse reaction.

Method

Assess baseline pulse for presence at the site (eg.radial), pulse rate and volume and assess skin colour and temperature. Assess capillary refill (normal < 2 secs) and assess systolic BP on basis of pulse site.

If the patient shows any evidence of very early hypovolaemia, i.e. tachycardia and cool skin, or injuries that will inevitably lead to significant blood loss, intravenous fluids should be considered. Only, however, after adequate airway and breathing resuscitation, and arrest of external haemorrhage, should infusion be considered. Obtaining IV access, and commencing volume replacement should routinely be achieved en route to hospital, and not induce delay at the scene.

Intravenous cannulation and fluid replacement should commence via at least 1 wide (14G – 16G) bore cannula, en route to hospital in all TIME CRITICAL PATIENTS, and **wherever possible** en route, with non-time critical patients, in those cases where IV access is indicated.

IV fluids should ideally be warmed.

Dosage and Administration

Adults

Administer or commence crystalloid 500 ml IV (rapid infusion) then reassess.

Aim to reduce tachycardia whilst restoring and maintaining a radial pulse (equivalent to a systolic BP of 80-90 mmHg). If there is significant improvement, slow to keep vein open (TKVO) rate and reassess regularly.

If no improvement, administer:

A further crystalloid 250 ml IV then reassess

If there has been a **significant improvement** in the patient's condition after the second administration (radial pulse returned and maintained), slow the infusion down to a TKVO rate and reassess regularly, otherwise continue fluids in 250 ml aliquots to 2 litres maximum

Only sodium chloride 0.9% should be considered in patients with diabetic hyperglycaemic ketoacidosis.

Children

Administer 20 ml/Kg, bolus then reassess,

If no improvement, administer:

A further 20ml/Kg, then reassess.

Additional Information

The vast majority of patients will be in hospital before the 2 litre maximum has been given. In the case of long journey times or entrapped patients, further fluids may need to be given to patients with severe blood loss. In TRAPPED patients skilled medical presence at the scene is **essential at the earliest stage to assist with volume replacement decisions.** On-line medical advise should be sought before infusing beyond 2 litres.

Continual reassessment avoids both UNDER and OVER infusion

Haemorrhage leads eventually to hypotension and a reduction in blood flow from the damaged vessels. Fragile clots will then form, but will be rapidly dislodged with a further haemorrhage if the BP is raised to over 80 – 90 mmHg by too much infused fluid. Aiming to maintain a systolic BP of 80 – 90 mmHg (radial pulse returns) ensures reasonable blood flow to heart, lungs, brain and kidneys, without risking clot disruption and re-bleeding.

Delay in removal to hospital must **not be prolonged by cannulating or infusing at the scene in non– trapped patients.**

Evidence suggests, in non-trapped patients, or those with journey times of less than 20 minutes, that pre-hospital fluid replacement produces little benefit to patients.

Appendix 3 Search Strategies

Clinical effectiveness: pre-hospital setting

COCHRANE CENTRAL REGISTER OF CONTROLLED TRIALS (ISSUE 4, 2002)

1 HEMORRHAGE*:ME
2 SHOCK-HEMORRHAGIC*:ME
3 SHOCK-TRAUMATIC*:ME
4 WOUNDS-AND-INJURIES*:ME
5 HYPOTENSION*:ME
6 HAEMORRHAG*
7 HEMORRHAG*
8 TRAUMA*
9 HYPOVOLAEMI*
10 HYPOVOLEMI*
11 (BLOOD next LOSS)
12 BLEEDING
13 ((((((((((#1 or #2) or #3) or #4) or #5) or #6) or #7) or #8) or #9) or #10) or #11) or #12)
14 FLUID-THERAPY*:ME
15 PLASMA-SUBSTITUTES*:ME
16 HYPERTONIC-SOLUTIONS*:ME
17 ISOTONIC
18 ISOTONIC-SOLUTIONS*:ME
19 INFUSIONS-INTRAVENOUS*:ME
20 REHYDRATION-SOLUTIONS*:ME
21 (FLUID next THERAPY)
22 (FLUID next ADMINISTRATION)
23 (FLUID next RESUSCITATION)
24 (FLUID next RESTORATION)
25 (FLUID next REPLACEMENT)
26 (FLUID next INFUSION)
27 (VOLUME next RESUSCITATION)
28 (VOLUME next REPLACEMENT)
29 (VOLUME next RESTORATION)
30 REHYDRATION
31 (INTRAVENOUS* near FLUID*)
32 COLLOIDS*:ME
33 COLLOID*
34 CRYSTALLOID*
35 DEXTRANS*:ME
36 ALBUMINS*:ME
37 STARCH*:ME
38 GELATIN*:ME
39 RINGER*
40 HARTMAN*
41 HAEMACCEL
42 HEMACCEL
43 ((((((((((((((((((((((((((#14 or #15) or #16) or #18) or #19) or #20) or #21) or #22) or #23) or #24) or #25) or #26) or #27) or #28) or #29) or #30) or #31) or #32) or #33) or #34) or #35) or #36) or #37) or #38) or #39) or #40) or #41) or #42)
44 EMERGENCY-MEDICAL-SERVICES*:ME
45 EMERGENCY-MEDICINE*:ME
46 EMERGENCY-TREATMENT*:ME
47 ALLIED-HEALTH-PERSONNEL*:ME
48 FIRST-AID*:ME

49 PARAMEDIC*
50 AMBULANCE*
51 (FIRST next AID*)
52 (LIFE and SUPPORT)
53 BTLS
54 ATLS
55 (EMERGENCY next SERVICE)
56 PREHOSPITAL
57 PRE-HOSPITAL
58 (ACCIDENT* near SCENE*)
59 (SPEED* near RESPONS*)
60 IMMEDIATE*
61 DELAY*
62 TIMELY
63 ((((((((((((((((((#44 or #45) or #46) or #47) or #48) or #49) or #50) or #51) or #52) or #53) or #54) or #55) or #56) or #57) or #58) or #59) or #60) or #61) or #62)
64 ((#13 and #43) and #63)

MEDLINE & PREMEDLINE (OVID, 1966-PRESENT, SEARCHED 10TH FEBRUARY 2003)

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized controlled trials/
4. random allocation/
5. double blind method/
6. single blind method/
7. or/1-6
8. (animal not human).sh.
9. 7 not 8
10. clinical trial.pt.
11. exp clinical trials/
12. (clin$ adj25 trial$).ti,ab.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
14. placebos/
15. placebo$.ti,ab.
16. random$.ti,ab.
17. research design/
18. or/10-17
19. 18 not 8
20. 19 not 9
21. comparative study/
22. exp evaluation studies/
23. follow up studies/
24. prospective studies/
25. (control$ or prospectiv$ or volunteer$).ti,ab.
26. or/21-25
27. 26 not 8
28. 26 not (9 or 20)
29. 9 or 20 or 28
30. exp shock, traumatic/ or exp shock, hemorrhagic/
31. exp hemorrhage/ or hemorrhag$.mp.
32. haemorrhag$.mp.
33. exp "wounds and injuries"/
34. trauma$.mp.
35. exp hypovolemia/
36. (hypovolem$ or hypovolaem$).mp.

37. blood loss.mp.
38. bleeding.mp.
39. penetrating.mp.
40. blunt.mp.
41. hypoten$.mp.
42. or/30-41
43. exp fluid therapy/ or fluid therapy.mp.
44. (fluid$ adj3 replace$).mp.
45. (fluid$ adj3 resuscitat$).mp.
46. (fluid$ adj3 infus$).mp.
47. (fluid$ adj3 administrat$).mp.
48. (volume adj3 replace$).mp.
49. (volume adj3 infus$).mp.
50. (volume adj3 resuscitat$).mp.
51. (intravenous$ adj3 fluid$).mp.
52. IV fluid$.mp.
53. (fluid$ adj3 restor$).mp.
54. (volume adj3 restor$).mp.
55. exp plasma substitutes/ or plasma substitut$.mp.
56. exp infusions, intravenous/
57. rehydration.mp.
58. exp colloids/
59. colloid$.mp.
60. crystalloid$.mp.
61. exp hypertonic solutions/
62. (hypertonic saline or hypertonic solution$).mp.
63. (isotonic saline or isotonic solution$).mp.
64. (ringer$ or hartman$).mp.
65. (albumin$ or gelatin$ or dextran$ or starch$ or Haemaccel or Hemaccel).mp.
66. or/43-65
67. exp Emergency Medicine/ or emergency medicine.mp.
68. exp emergency medical services/
69. exp emergency treatment/ or emergency treatment$.mp.
70. pre-hospital.mp.
71. prehospital.mp.
72. exp allied health personnel/ or paramedic$.mp.
73. exp first aid/ or first aid.mp.
74. ambulance$.mp.
75. life support.mp.
76. immediate$.mp.
77. delay$.mp.
78. (speed$ adj3 response$).mp.
79. (scene adj3 accident$).mp.
80. timely administration.mp.
81. (BTLS or ATLS).mp.
82. or/67-81
83. 29 and 42 and 66 and 82
84. limit 83 to human

EMBASE (OVID, 1980-PRESENT, SEARCHED 10TH FEBRUARY 2003)

1. randomized controlled trial/
2. exp clinical trial/
3. exp controlled study/
4. double blind procedure/
5. randomization/
6. placebo/
7. single blind procedure/

8. (control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp.
9. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp.
10. (placebo$ or matched communities or matched schools or matched populations).mp.
11. (comparison group$ or control group$).mp.
12. (clinical trial$ or random$).mp.
13. (quasiexperimental or quasi experimental or pseudo experimental).mp.
14. matched pairs.mp.
15. or/1-14
16. exp traumatic shock/
17. exp hypovolemic shock/
18. exp hemorrhagic shock/
19. trauma$.mp.
20. (hypovolem$ or hypovolaem$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
21. (haemorrhag$ or hemorrhag$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
22. exp injury/ or exp wound/
23. exp hypotension/
24. exp hypovolemia/ or exp hemorrhage/
25. hypotens$.mp.
26. exp bleeding/ or bleeding.mp.
27. blood loss.mp.
28. penetrating.mp.
29. blunt.mp.
30. or/16-29
31. fluid therapy.mp. or exp fluid therapy/
32. (fluid$ adj3 replace$).mp.
33. (fluid$ adj3 resuscit$).mp.
34. (fluid$ adj3 infus$).mp.
35. (fluid$ adj3 administrat$).mp.
36. (volume adj3 replace$).mp.
37. (volume adj3 infus$).mp.
38. (volume adj3 resuscit$).mp.
39. (intravenous$ adj3 fluid$).mp.
40. IV fluid$.mp.
41. (fluid$ adj3 restor$).mp.
42. (volume adj3 restor$).mp.
43. plasma substitut$.mp. or exp plasma substitute/
44. rehydrat$.mp. or exp rehydration/
45. exp colloid/
46. exp crystalloid/
47. (colloid$ or crystalloid$).mp.
48. (hypertonic saline or hypertonic solution$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
49. (isotonic saline or isotonic solution$).mp.
50. exp hypertonic solution/
51. (ringer$ or hartman$).mp.
52. (albumin$ or gelatin$ or dextran$ or starch$ or Haemaccel or haemaccel).mp.
53. or/31-52
54. exp emergency medicine/ or emergency medicine.mp.
55. emergency medical service$.mp. or exp emergency health service/
56. emergency treatment$.mp. or exp emergency treatment/
57. prehospital.mp.
58. pre-hospital.mp.
59. exp paramedical personnel/ or paramedic$.mp.
60. first aid$.mp. or exp first aid/
61. ambulance$.mp.
62. life support.mp.
63. immediate$.mp.

64. delay$.mp.
65. (speed$ adj3 response).mp.
66. (scene adj3 accident).mp.
67. timely administrat$.mp.
68. (BTLS or ATLS).mp.
69. or/54-68
70. 15 and 30 and 53 and 69
71. limit 70 to human

SCIENCE CITATION INDEX (WEB OF SCIENCE, 1980-PRESENT, SEARCHED 10TH FEBRUARY 2003; SEARCH TERMS LIMITED TO 50)

(random* or trial* or blind* or prospective* or control* or comparison or evaluation) and

(trauma* or injur* or wound* or hypotens* or hypovolaemi* or hypovolemi* or haemorrhag* or hemorrhag* or blood loss or bleeding or shock) and

(fluid* therapy or fluid* resuscitat* or fluid* replace* or fluid* administrat* or fluid* infus* or fluid* restor* or intravenous* fluid* or IV fluid* or volume replace* or volume resuscitat* or volume restor* or plasma substitut* or rehydrat* or colloid* or crystalloid* or Ringer* or Hartman* or albumin* or gelatin* or dextran*) and

(pre-hospital or prehospital or emergency or first aid or paramedic* or accident* or ambulance* or life support or immediate* or delay* or BTLS or ATLS)

WEB SITES SEARCHED (20TH JANUARY 2003)

MetaRegister/Current Controlled Trials: http://www.controlled-trials.com

National Research Register: http://www.update-software.com/national/

Trauma.org: http://www.trauma.org

West Midlands Accident & Emergency Surveillance Centre:
http://www.bham.ac.uk/Publichealth/accidentandemergencycentre/index.htm

Emergency Medicine Research Group: http://medweb.bham.ac.uk/emerg

Emergency Medical Services-The Journal of Emergency Care, rescue and Transportation:
http://emsmagazine.com/articles/index.html

Clinical effectiveness: any setting

COCHRANE CENTRAL REGISTER OF CONTROLLED TRIALS ISSUE 1, 2003)

1 HEMORRHAGE
2 SHOCK HEMORRHAGIC
3 SHOCK TRAUMATIC
4 WOUNDS AND INJURIES
5 HYPOTENSION
6 haemorrhag*
7 hemorrhag*
8 trauma*
9 hypovolaemi*
10 hypovolemi*

11 (blood next loss)
12 bleeding
13 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12)
14 FLUID THERAPY
15 PLASMA SUBSTITUTES
16 HYPERTONIC SOLUTIONS
17 ISOTONIC SOLUTIONS
18 INFUSIONS INTRAVENOUS
19 rehydration
20 REHYDRATION SOLUTIONS
21 isotonic
22 (fluid next therapy)
23 (fluid next administration)
24 (fluid next resuscitation)
25 (fluid next restoration)
26 (fluid next replacement)
27 (fluid next infusion)
28 (volume next resuscitation)
29 (volume next replacement)
30 (volume next restoration)
31rehydration
32 (intravenous* near fluid*)
33 colloid*
34 crystalloid*
35 ringer*
36 hartman*
37 haemaccel
38 hemacell
39 COLLOIDS
40 DEXTRANS
41 ALBUMINS
42 STARCH
43 GELATIN
44 (#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43)
45 (#13 and #44)

MEDLINE & PREMEDLINE (OVID, 1966-PRESENT, SEARCHED 1st APRIL 2003)

1 randomized controlled trial.pt. (171724)
2 controlled clinical trial.pt. (62605)
3 randomized controlled trials.sh. (27467)
4 random allocation.sh. (47621)
5 double blind method.sh. (72642)
6 single-blind method.sh. (7076)
7 or/1-6 (291122)
8 (animal not human).sh. (2652210)
9 7 not 8 (277097)
10 exp shock,traumatic/ or exp shock, hemorrhagic/ (9755)
11 exp hemorrhage/ or hemorrhag$.mp. (177921)
12 haemorrhag$.mp. (21226)
13 exp "wounds and injuries"/ (393854)
14 trauma$.mp. (116395)
15 exp hypovolemia/ (197)
16 (hypovolem$ or hypovolaem$).mp. (4453)
17 blood loss.mp. (12188)
18 bleeding.mp. (60961)
19 penetrating.mp. (12544)

20 blunt.mp. (11993)
21 hypoten$.mp. (41551)
22 or/10-21 (679903)
23 exp fluid therapy/ or fluid therapy.mp. (8820)
24 (fluid$ adj3 replace$).mp. (1559)
25 (fluid$ adj3 resuscitat$).mp. (1917)
26 (fluid adj3 infus$).mp. (1714)
27 (fluid$ adj3 administrat$).mp. (2371)
28 (volume adj3 replace$).mp. (1031)
29 (volume adj3 infus$).mp. (1873)
30 (volume adj3 resuscitat$).mp. (581)
31 (intravenous$ adj3 fluid$).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (2457)
32 iv fluid$.mp. (461)
33 (fluid$ adj3 restor$).mp. (380)
34 (volume adj3 restor$).mp. (675)
35 exp plasma substitutes/ or plasma substitut$.mp. (23556)
36 exp infusions, intravenous/ (28982)
37 rehydration.mp. (3485)
38 exp colloids/ (51120)
39 colloid$.mp. (19477)
40 crystalloid$.mp. (3044)
41 exp hypertonic solutions/ (8053)
42 hypertonic saline.mp. (2689)
43 hypertonic solution$.mp. (5109)
44 isotonic saline.mp. (2080)
45 isotonic solution$.mp. (5030)
46 ringer$.mp. (9166)
47 hartman$.mp. (1610)
48 (albumin$ or gelatin$ or dextran$ or starch$ or Haemaccel or Hemaccel).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (148039)
49 or/23-48 (279414)
50 9 and 22 and 49 (1806)
51 exp BURNS/ (30667)
52 50 not 51 (1725)
53 exp Shock, Septic/ (11737)
54 52 not 53 (1707)
55 limit 54 to human (1704)
56 from 55 keep 1-200 (200)

EMBASE (OVID, 1980-PRESENT, SEARCHED 1st APRIL 2003)

1 randomized controlled trial/ (73065)
2 exp clinical trial/ (266463)
3 exp controlled study/ (1546132)
4 double blind procedure/ (47155)
5 randomization/ (5827)
6 placebo/ (62426)
7 single blind procedure/ (4094)
8 or/1-7 (1688241)
9 exp traumatic shock/ (633)
10 exp hypovolemic shock/ (828)
11 exp hemorrhagic shock/ (2832)
12 trauma$.mp. (86990)
13 (hypovolem$ or hypovolaem$).mp. (4692)
14 (haemorrhag$ or hemorrhag$).mp. (69684)
15 exp injury/ or exp wound/ (387199)
16 exp hypotension/ (31222)

17 exp hypovolemia/ or exp hemorrhage/ (114856)
18 hypotens$.mp. (42367)
19 exp bleeding/ or bleeding.mp. (136216)
20 blood loss.mp. (9814)
21 penetrating.mp. (9556)
22 blunt.mp. (9578)
23 or/9-22 (602778)
24 fluid therapy.mp. or exp fluid therapy/ (19097)
25 (fluid$ adj3 replace$).mp. (1322)
26 (fluid$ adj3 resuscitat$).mp. (1808)
27 (fluid adj3 infus$).mp. (1418)
28 (fluid$ adj3 administrat$).mp. (1717)
29 (volume adj3 replace$).mp. (897)
30 (volume adj3 infus$).mp. (1589)
31 (volume adj3 resuscitat$).mp. (540)
32 (intravenous$ adj3 fluid$).mp. (3038)
33 iv fluid$.mp. (362)
34 (fluid$ adj3 restor$).mp. (303)
35 (volume adj3 restor$).mp. (540)
36 plasma substitut$.mp. or exp plasma substitute/ (16613)
37 rehydrat$.mp. or exp rehydration/ (3672)
38 exp colloid/ (4123)
39 exp crystalloid/ (1248)
40 (colloid$ or crystalloid$).mp. (17219)
41 hypertonic saline.mp. (2231)
42 hypertonic solution$.mp. (1732)
43 isotonic saline.mp. (1711)
44 isotonic solution$.mp. (817)
45 exp hypertonic solution/ (1314)
46 (ringer$ or hartman$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (9218)
47 (albumin$ or gelatin$ or dextran$ or starch$ or Haemaccel or Hemaccel).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (99728)
48 or/24-47 (160067)
49 8 and 23 and 48 (6535)
50 limit 49 to human (3460)
51 exp BURN/ (15790)
52 50 not 51 (3293)
53 exp Septic Shock/ (7521)
54 52 not 53 (3233)

SCIENCE CITATION INDEX (WEB OF SCIENCE, 1980-PRESENT, SEARCHED 31ST MARCH 2003)

(random* or trial* or blind*) and

(trauma* or injur* or wound* or hypotens* or hypovolaemi* or hypovolemi* or haemorrhag* or hemorrhag* or blood loss or bleeding or shock) and

(fluid* therapy or fluid* resuscitat* or fluid* replace* or fluid* administrat* or fluid* infus* or fluid* restor* or intravenous* fluid* or IV fluid* or volume replace* or volume resuscitat* or volume restor* or plasma substitut* or rehydrat* or colloid* or crystalloid*)

Search strategies systematic reviews

Search filters for systematic reviews were used for MEDLINE and EMBASE searches and combined with relevant text and MeSH words. Only relevant text and MesH words were required to search for systematic reviews in the Cochrane library. Searches were run in March 2003. There were no language restrictions. Full details of the search strategies can be obtained from the authors on request.

Cost-effectiveness search

Search strategy

In order to identify relevant economic evaluations the following sources were searched:

- Bibliographic databases : Cochrane Library (NHS EED and DARE) Issue 2 2003, MEDLINE (Ovid) 1980-June 2003 , EMBASE (Ovid) 1980 – June 2003 . The OHE Health Economic Evaluations Database (June 2003 update) was also searched.

MEDLINE and EMBASE were searched for relevant cost and cost effectiveness studies by employing a broad search strategy combining both subject index terms limited by economic subheadings and relevant textwords in combination with selected economic index terms. The specialised health economic sources were searched using a combination of relevant subject terms only, given the specialised nature of the databases. There were no language restrictions. Full details of the search strategies are listed below:

COCHRANE LIBRARY (DARE and NHS EED) 2003 Issue 2

1 paramedic*
2 als
3 bls
4 atls
5 btls
6 emt*
7 prehospital
8 pre-hospital
9 (accident near scene)
10 exp EMERGENCY MEDICAL SERVICES/
11 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8)

MEDLINE (OVID, 1980 – PRESENT, SEARCHED 26 June 2003)

1 exp Emergency Medical Technicians/ec [Economics] (59)
2 exp Allied Health Personnel/ec [Economics] (541)
3 exp AMBULANCES/ec [Economics] (182)
4 exp Allied Health Personnel/ec [Economics] (541)
5 ems.mp. (4012)
6 (atls or btls or als or bls or phtls).mp. (5610)
7 paramedic$.mp. (2920)
8 (pre adj hospital).mp. (767)
9 (ambulance adj technician$).mp. (17)
10 (trauma adj care).mp. (1035)
11 (trauma adj resuscitation).mp. (121)
12 (emergency adj2 technician$).mp. (430)
13 or/1-4 (721)
14 or/5-12 (13983)

15 exp economics/ (316873)
16 exp "costs and cost analysis"/ (106487)
17 exp health care costs/ (20474)
18 exp economics medical/ (9838)
19 exp cost-benefit analysis/ (32526)
20 or/15-19 (316873)
21 14 and 20 (555)
22 13 or 21 (1240)
23 limit 22 to yr=1980-2003 (1147)

EMBASE (OVID, 1980 – PRESENT, SEARCHED 26 June 2003)

1 emergency medical technicians.mp. or exp Rescue Personnel/ (813)
2 exp Paramedical Personnel/ (34526)
3 exp Patient Transport/ or exp Resuscitation/ or exp Emergency Health Service/ or exp Paramedical Education/ or exp Paramedical Personnel/ or paramedic$.mp. or Emergency Medicine/ or exp Ambulance/ (65202)
4 (pre adj hospital).mp. (553)
5 (ambulance adj technician$).mp. (9)
6 (trauma adj care).mp. (741)
7 (trauma adj resuscitation).mp (108)
8 (emergency adj technician$).mp. (2)
9 (ats or bts or atls or btls or phtls or ems).mp. (3685)
10 or/1-9 (68677)
11 cost benefit analysis/ (15884)
12 cost effectiveness analysis/ (29746)
13 cost minimization analysis/ (537)
14 cost utility analysis/ (840)
15 economic evaluation/ (1535)
16 (technology adj assessment$).tw. (963)
17 or/11-16 (45693)
18 10 and 17 (1612)

HEALTH ECONOMIC EVALUATIONS DATABASE (OHE), SEARCHED June 2003

Textwords used : paramedic$ or als or bls or atls or btls or phtls or pre-hospital or pre hospital or emergency medical technician$ or ambulance$. No specific economic or cost terms used given subject content of database.

Appendix 4 Appraisal of observational studies

Critical Appraisal of Demetriades et al (1996)[50]

Study Design:
This paper reports a retrospective cohort study of outcomes for all patients transported in 1992 and 1993 to a large, urban, trauma centre in Los Angeles who met the criteria for major trauma

Questions addressed by study:
Is there a difference in survival of patients with severe trauma between those transported to hospital by paramedics trained in ALS compared to those who are transported by non-EMS methods?

Population:
All patients transported to an urban trauma centre who met the criteria for major trauma (including BP<90 mmHg, penetrating injuries, blunt injuries, head injuries and falls >15ft) during 1992 and 1993.

The trauma centre was a large academic centre serving a large urban population in Los Angeles.

Intervention/exposure:
Patients transported to hospital by paramedics trained and equipped to undertake ALS (EMS)

Comparator:
Patients transported by non-paramedics (e.g. friends, relatives, bystanders or police) (non-EMS)

Outcome:
Mortality

Results:
5782 patients fulfilled criteria (4856 (84%) EMS, 926 (16%) Non-EMS) and 4874 EMS patients and 297 non-EMS transport patients having sufficient data for inclusion in the analysis.

The crude mortality rates were 9.3% EMS and 4% Non-EMS ($p<0.001$). This gives a crude relative risk of death of 2.32 (95%CI 1.67-3.22). It this is adjusted for Injury Severity Score ISS) this is reduced to 1.60 (95%CI 1.18 to 2.15)

After controlling for 6 confounding factors (age, gender, cause of injury, mechanism of injury, severe head trauma status and ISS group stated) the adjusted mortality rate for those with an ISS >15 was 28.2% in the EMS group compares with 17.9% in the Non-EMS group ($p<0.001$). (RR 1.57)

Potential problems with the study:

1. The numbers of patients in the table disagree with the numbers in the text (e.g. more EMS patients in table)
2. It is not clear to what extent the data from the non-EMS group is truly representative of this group as it appears that over 2/3rds of these patients were excluded from the analysis (presumably because they had over 10% of variables missing), while virtually none were from the EMS group.
3. The groups are clearly different from each other in both demographic and injury characteristics with the EMS patients being the more severely injured group on the whole, although head injury was more severe in the privately transported group.
4. Even though stratified and adjusted analyses are done it is possible that observed differences in outcomes were due to unknown confounders and remaining unadjusted differences in severity.
5. The text says 9 confounders were included in the analysis but only 6 covariates are mentioned.
6. It is not possible to distinguish between the effects of time delay and the effects of the interventions of paramedics:
    a. Important time variables were not included in the analysis because the time of injury was recorded in only 21% of cases.
    b. In the discussion section the authors mention other work that they have undertaken on pre-hospital times and comment "It is likely that patients brought in by bystanders reach the hospital for definitive treatment more than 30 minutes earlier than those brought in by EMS".
    c. No data on IV fluid administration is recorded.

External generalisability:
The degree of generalisability of this study to a rural population with longer transport times is not clear. It should also be remembered that the US has a different pattern of injury than the UK with penetrating to blunt trauma in the US having a ratio of ~1:1 but 1:10 in the UK.

Conclusions
The limitations of this study are a consequence of the design and data available rather then poor conduct of the study. The study demonstrates that there is poorer survival in major trauma patients transported to hospital by EMS than in those brought in by other people. There is a clear and significant difference that persists after adjustment for known confounders such as severity of injury. While the study is suggestive that there may be real difference in outcome depending on transport method (with the emergency medical services having the poorer outcome), it is not possible to say conclusively whether the observed adjusted difference is due to uncontrolled confounding or a true difference in the effect of transport method and, if it is a real effect, the data does permit estimation of the relative contributions to survival differences from delay to definitive treatment and pre-hospital interventions.

Critical Appraisal of Jacobs LM et al (1984)[5]

Study Design:
This paper reports a prospective cohort study of trauma patients transported to Boston City Hospital by emergency medical services either by ALS ambulances or BLS ambulances.

Questions addressed by study:
1. Does ALS produce more positive changes in the Trauma Score (TS) by time of arrival at hospital than BLS?
2. Does increase in Trauma Score correlate with survival?

Population:
All trauma patients transported to Boston City Hospital who met one or more of the following criteria during a six month period in 1981 were entered into the study:
- In shock (defined as systolic BP <100 mmHg)
- Penetrating injury of the chest, abdomen, head, neck or groin
- Head injury with depressed level of consciousness
- Any injury involving two or more body systems each with an ISS greater than one
- Fall greater than 15 feet
- Deep burns over 15% of surface area

Intervention/comparator:
ALS vs. BLS

(The primary ALS intervention was IV fluid resuscitation, which was received by 88% of patients.)

Outcome:
Change in Trauma Score from when patient attended at scene to that on arrival in hospital

Potential problems with the study:
1. During the daytime patients are selected to be transported by ALS or BLS on the basis of information given to the emergency dispatch communications centre. (There was only BLS cover at night.) Therefore the patients receiving ALS were potentially more severely injured than those getting BLS. Thus differences in survival and changes in TS are difficult to interpret as due both known and unknown confounders.
2. That the two groups are not comparable at baseline is confirmed by the worse Trauma Score and Injury Severity Score of the ALS patients. Moreover 13/80 ALS patients had a severe Trauma Score of 1-3 compared to only 5/98 in the BLS group.
3. The Trauma Score is a physiological measure of a patient's response to injury that can be undertaken at the scene using common cardiovascular, respiratory, and neurological measures (BP, respiratory rate, and the Glasgow Coma Scale). The problem with using an improvement in this score as a measure of physiological improvement is that it conflates natural improvement (e.g. because a patient is improving, or compensating well or simply because of regression to the mean), which will be associated with improved outcome with changes induced by treatment that may or may not be correlated with improved outcome.
4. Although the authors go on to do a regression analysis purporting to show that the positive change in the original TS is correlated with survival they fail to make this

distinction. Moreover, although the reporting of the logistic regression model is incomplete, the text is suggestive that the exposure (ALS or BLS) may not have been included.

5. There is a ceiling effect in that the study reports the improvement in trauma score, so that patients who have a relatively good trauma score (14-16) have little room for improvement (the Trauma Score goes from 1 (most severe) to 16 (least severe). Since 59% of BLS patients are in the less severe group compared to only 41% of ALS patients, any difference in change in TS could be just a function of the baseline imbalance in severity of TS between the two groups.
6. There is no record of blinding of researcher to outcome information.
7. The authors do not report the true endpoint of interest (mortality rates) for the two groups. However the figure 2 shows that there were no survivors in scores 1-3 suggesting that there were probably more deaths in the ALS group despite the stated superiority in number with improved Trauma Score.
8. The authors fail to distinguish between statistically significant and clinically significant differences in both confounders and outcomes. Sometimes only reporting the p-values and not the results themselves.
9. They appear to confuse absence of evidence (e.g. non significant p-values on relationship between hospital transport times and mode of transport) with evidence of absence, which in the light of 8 above is impossible to further evaluate.
10. The sample size was small and the study probably did not have the power to demonstrate clinically significant differences.

Conclusions

This paper provides little evidence to inform the ALS vs BLS debate. The authors' conclusion "that appropriate field ALS resuscitation results in more favourable outcomes following major trauma" is not supported by the reported results.

Critical Appraisal of Nicholl et al (1998)[16]

Study Design:
This paper reports a prospective cohort study of outcomes for trauma patients attended by either an EMT-only crew or a crew with at least one trained paramedic in three different areas of England during 1994 to 1996. Patients from two of the areas were sampled and all patients from the third area included. Inclusion/exclusion criteria were applied retrospectively.

Questions addressed by study:
Is there a difference in outcomes (mortality, morbidity, QoL) for patients attended by paramedics compared to EMT-only crews?

Population:
Sample of trauma patients attended by paramedic or EMT-only crews in three areas of England 1994-1996 (variable start/end dates for different areas). Patients were included if: admitted to hospital >2 nights; admission to ICU/HDA; died after arrival of ambulance if trauma was listed as a cause of death; died of injuries where trauma listed as a cause of death; re-admitted >2 days after incident for treatment of original trauma injuries; died within 6 months where trauma listed as a cause of death. Exclusion criteria included dead before arrival of ambulance, and patients involved in 'major incidents' as defined by each respective ambulance service.

The three areas covered different types of urban, suburban and rural areas.

Intervention/exposure:
Patients attended at scene by paramedics trained and equipped to undertake ALS.

Comparator:
Patients attended at scene by EMT-only crews.

Outcome:
Treatments given on scene, time on scene, mortality, morbidity, QoL.

Results:
2,045 of the sampled patients fulfilled the criteria; 605 EMT-only, 1440 paramedic attended were included' There were 47 cases where the type of crew was unknown.

For procedures available to both types of crew, crews including at least one paramedic gave slightly more treatment on scene compared to EMT-only crews. Procedures used only by paramedics were common in the paramedic-attended group, with cannulation attempted in around a third of patients and intubation in 2%; 10% were given drugs. (based on only 868/1440 paramedic cases with completed PRFs).

Time on scene was an average of 2 minutes greater for crews including a paramedic, for both crude and adjusted analyses. The additional time on scene appeared entirely due to time spent on patients who received paramedic-only interventions, these interventions adding 10-13 minutes on average.

Counterintuitively, mortality was inversely related to travel time, with mortality consistently reducing with decreased total travel time. The relationship with distance from hospital did not follow a similar pattern (with highest mortality at moderate distances, and lower mortality at both shorter and longer distances). These relationships are hard to interpret as they may reflect the time of day, the perceived urgency of the case, and the traffic/road environment.

Crude mortality rates were higher in the paramedic-attended patients, with a crude OR of 1.34 (0.86 – 2.11) and adjusted OR of around 1.8 (0.9 – 3.7). The pattern of increased mortality for paramedic-attended scenes was not consistent across the different areas, with an OR of 3.1 in Area 1 and 0.78 in Area 3. The authors attribute this to case-mix and different targeting of paramedics in the areas.

There were no differences in ICU admissions or in length of hospital stay. SF-36 scales tended to favour paramedic-attended patients, although it is not possible to separate this observation out from a survivor effect (where the arm with a higher mortality is left with only relatively healthy patients to complete QoL forms), and the fact that this study was conducted in a small sub-sample of patients sent the 6 month follow-up questionnaire with only 67% responding.

Potential problems with the study:

1. The inclusion/exclusion criteria are based largely on outcomes, especially death and length of admission. This would lead to a heavily biased sample if deaths on one arm were more likely to occur earlier and/or in hospital compared to the other arm, or if information were better recorded on one arm compared to the other. In this case both biases are likely to include more patients with adverse outcomes on the paramedic-attended arm. In addition, where a doctor was present at EMT-only attended scenes, deaths in these patients were excluded from the analysis; no such exclusions were made for the paramedic-attended group.
2. There is very little consideration of the possible selection biases; adjusted analyses are presented but the contribution of unknown confounders is not fully considered. In particular it appears that a much higher proportion of paramedic-attended patients were considered eligible for the study, which might reflect a greater likelihood of a paramedic attending for serious cases and the potential biases in the inclusion/exclusion criteria for the study.
3. On-scene data were poorly recorded in two of the three areas.
4. Numbers included in various analyses is not always clear and there are clearly incorrect numbers in some of the tables.
5. There is limited discussion of the counter-intuitive inverse relationship between travel time and mortality, whilst delay-on-scene is discussed extensively as a factor likely to contribute to death. Travel time is not summarised by type of crew, and other similar related confounders do not appear to have been fully explored.
6. The relative risk of death overall appears largely due to a higher relative risk of death for paramedic-attended patients with an ISS <15 (less severe injury) or no head injury. No attempt is made to explain this finding or any selection bias, which might have contributed to this effect. The authors go on to state that the excess risk also appears to be confined to patients in whom blood loss might have been a problem, noting that the relative risk of death from the pooled categories of hypovolaemic

shock/recurrent haemorrhage, multiple fractures and injuries to thorax abdomen account for all the excess deaths in the paramedic-attended arms. There is no discussion of how this might relate to the finding for less seriously injured and non-head-injured patients.

External generalisability:
The three areas are not described in great detail except that statement that they include metropolitan, urban, suburban and rural areas. It is not clear how the population structure and/or ambulance services reflect the UK as a whole.

Conclusions:
The study findings are interesting but unfortunately it is not possible to conclude anything due to the biases in the design and conduct of the research. Of particular concern is the use of outcomes (death, length of hospital stay, ICU admission) as criteria for inclusion/exclusion, and the exclusion of EMT-only deaths where a doctor was in attendance, as well as the large quantity of missing data, especially in the EMT-only group, which may have affected inclusion/exclusion decisions. The one convincing finding of the study is that paramedics tend to give more interventions on-scene and that this contributes to a substantial delay in getting patients to hospital. This finding, however, is difficult to interpret given the uncertainties over differences in case-mix. Furthermore, the inverse relationship between travel time and mortality also found is not satisfactorily discussed or accounted for in subsequent analyses.

Critical Appraisal of Pepe et al (1987)[51]

Study Design:
This paper reports a 2½ year prospective cohort study of consecutive victims of penetrating trauma and haemorrhagic shock looking at survival rates.

Questions addressed by study:
What is the relationship between survival rates of patients with haemorrhagic shock due to penetrating injuries and total pre-hospital time required to manage and deliver those patients to a single regional trauma centre.

Population:
Patients presenting with penetrating injury and a systolic blood pressure of 90 mmHg or less who transported to a large urban regional trauma centre in Houston, USA.

Intervention/exposure:

Comparator:

Outcome:
Survival (discharge from hospital alive).

Results:
498 consecutive patients met the entry criteria. Patients were stratified into four groups according to their initial pre-hospital trauma score (1, 2-6, 7-11, 12-15) for analysis. The pre-hospital time was arbitrarily divided into four periods (0-20, 21-30, 31-40 and over 40 minutes). The probability of survival for all patients was assessed using the TRISS methodology, based on age, mechanism of injury, injury severity (ISS), and the trauma score (TS). Trauma score as predicted correlated with survival, however this did not increase with total pre-hospital time.

Potential problems with the study:

1. As part of a concomitant protocol 254 of the patients also had a pneumatic antishock garment applied on a random basis. This may have altered transport times and be systematically associated with a different outcome, thereby confounding any analysis using pre-hospital times.
2. Analysis used arbitrary groupings for continuous variables, thereby losing power. It is not clear why a regression approach was not used that could have incorporated the original continuous (rather than grouped values) and would have allowed a direct comparison of survival rates.
3. The groups are very small. In group 1 where the predicted survival was only 2% then it is not surprising that with four groups with a total of n=35 that no trend could be demonstrated. In Group TS=7-11 there are 102 patients and there is an increase in the percentage dying with pre-hospital time. The fact that this is not statistically significant does not mean that there is not a true effect here.

Conclusions
The study is too underpowered to be able to demonstrate whether there is or is not relationship between pre-hospital time and death rates, exacerbated by a failure to use

appropriate statistical methods.. The authors conflate absence of evidence with evidence of absence.

Critical Appraisal of Sampalis et al (1997)[44]

Study Design:
This paper reports a retrospective cohort study of outcomes comparing patients who received IV fluids and those who did not. The patients were matched by pre-hospital index score (PHI) to try to produce comparable groups. (This measure was chosen because it was a physiological score based on BP, respiratory rate, pulse, level of consciousness and presence of penetration injury and was thought to be more appropriate than an anatomically based instrument such as the ISS.)

Questions addressed by study:
Is the survival of severely injured patients who received IV fluids different from those who did not?

Population:
360 severely injured patients from a prospective study of pre-hospital care in Montreal conducted in 1987 plus second cohort of severely injured patient transported to the Montreal General Hospital Trauma Centre between April 1993 and December 1994.

Intervention/exposure:
IV fluids

Comparator:
No IV fluids

Outcome:
Mortality

Results:
The mortality rates for the IV and no-IV groups were 23% and 6% respectively (Crude unmatched OR 5.11 (95%CI 2.6 – 9.9); Matched OR 8.6 (95%CI 3.4 – 21.7)) . However, despite matching on PHI the groups were very different with more severely injured patients in the IV group. The technique for logistic regression used to adjust for confounding is not described in full but was said to adjust for age, sex, ISS, mechanism of injury and pre-hospital time. The adjusted OR for death was 2.33 (95%CI 1.02 – 5.28, p = 0.04). A test for interaction between pre-hospital time and IV fluid replacement was not found to be significant (p=0.80) despite the fact that an analysis stratified into three groups by pre-hospital time was suggestive of an increasing risk of death in the IV fluids group as pre-hospital time increased.

Potential problems with the study:
This is an observational study and despite matching by PHI the two groups compared are substantially different. The change in the crude OR for death from 8.6 to 2.33 after adjustment for known confounders is large. It could well be that unknown confounding, especially related to the physician assessment of prognosis, could account for the observed OR of 2.33. In this respect it must be noted that in 65% of cases where no IV fluids were given a physician who could have given them was present and chose not to do so.

Conclusions

The limitations of this study are a consequence of the design and data available rather then poor conduct of the study. The IV fluid group had a clearly different pattern and severity of injury than the no IV fluid group. The way in which patients are selected in the field to receive IV fluids or not means that there is clearly the possibility of further bias that may not have been accounted for by adjustment for the measured confounders. The authors conclude that their findings are consistent with the hypothesis that early IV fluid replacement is harmful. However, while the study provides no evidence to support the use of IV fluids, and the IV fluid group had worse outcomes, the weaknesses of the observational design and the dissimilarity between the groups compared are so great that it is not possible to reliably judge whether the IV fluids were in fact doing harm.

Appendix 5 Appraisal of systematic reviews

Review: Liberman *et al*, 2000[32]

Criteria	Comment
Main characteristics:	
Population	Trauma patients
Intervention	Pre-hospital ALS
Comparator	Pre-hospital BLS
Outcomes	Mortality
Date of completion of searches	1998
Search strategy (databases used, language restrictions, citation searching, handsearching)	Search limited to MEDLINE database (range of keywords used; no details on language restrictions)
Types of studies included (RCTs only, observational studies included)	RCTs and observational studies
Inclusion and exclusion criteria (clearly defined, applied by more than one reviewer)	Inclusion criteria: studies must contain numerical data of on-scene time, number of deaths in ALS and BLS patients, predicted mortality rates, intravenous access and fluid administration data or endotracheal intubation data. Inclusion for mortality analysis: ALS and BLS data, number of deaths in each group stated, indicator of injury severity; not clear if criteria were defined before selection Inclusion and exclusion performed by one reviewer
Data extraction (process, performed by more than one reviewer)	Data extracted by one reviewer
Quality assessment (was it performed, what were the criteria)	Points awarded for design and methodological criteria; not clear if validated scales Of 15 studies used for mortality data, 13 were observational Quality for design and methodology was variable 1 study (Martin 1992) appears to be a preliminary report of Bickell 1994; the author appears to have treated these as separate studies
Quantity of studies identified	49 relevant studies identified; 15 of these used for mortality analysis
Synthesis of results (were results pooled, was clinical or statistical heterogeneity assessed, sub-group analyses)	Odds ratios (95% confidence intervals) calculated on basis of published mortality or survival data; OR>1 signifies increased odds of death for ALS patients; odds ratios were calculated for sub-groups according to study design and methodological quality; no assessment of statistical or clinical heterogeneity
Direction of effect	Based on RCTs and observational studies: 3/15 studies favoured ALS, 12/15 favoured BLS in terms of mortality. The overall crude OR was 2.92 (favouring BLS). Studies with a good design gave an OR 1.89 (favouring BLS to a lesser extent). Confidence intervals were not stated
Summary (key findings and validity)	It is possible that some studies were missed, as the search strategy was not very comprehensive; some of the included studies had poor study designs and weak methodology; there was no assessment of clinical and statistical heterogeneity between studies before they were pooled; overall direction of effect is towards BLS being more effective in preventing deaths than ALS (although it is not clear if this is statistically significant); this effect is less pronounced for studies with higher design quality; it is not clear to which extent confounding in the individual studies is contributing to this result, although the author has attempted to adjust for this

Review: Sethi *et al*, 2003[33]

Criteria	Comment
Main characteristics:	
Population	Trauma patients
Intervention	Ambulance crews with ALS training
Comparator	Ambulance crews with any other level of training
Outcomes	Mortality
Date of completion of searches	2000
Search strategy (databases used, language restrictions, citation searching, handsearching)	Comprehensive search strategy (several databases searched , no language restrictions, reference lists checked, authors contacted)
Types of studies included (RCTs only, observational studies included)	RCTs, quasi-randomised studies and controlled before-and-after studies
Inclusion and exclusion criteria (clearly defined, applied by more than one reviewer)	Inclusion criteria defined before selection (trauma patients, ambulance crews with ALS training versus ambulance crews with any other level of training, death from all causes, morbidity) Identified abstracts assessed by two reviewers
Data extraction (process, performed by more than one reviewer)	Data extraction performed independently by two reviewers on type of design, stratification for confounders, method of allocation concealment, number of randomised patients, types of participants, interventions and outcomes)
Quality assessment (was it performed, what were the criteria)	Quality was assessed according to selection, performance, exclusion or detection bias, method of allocation, degree of follow-up and soundness of assessments; Methodological quality of the 1 identified study was poor: there was poor compliance with the protocol and only 16 patients were randomised who were subsequently added to the main (non-randomised) cohort of 2000 patients
Quantity of studies identified	1 RCT was identified, however the results were analysed for patient cohorts as very few patients were randomised
Synthesis of results (were results pooled, was clinical or statistical heterogeneity assessed, sub-group analyses)	N/A
Direction of effect	There was a non-significant increase in mortality in those patients attended by paramedics compared to those attended by emergency medical technicians based on the analysis of the cohort
Summary (key findings and validity)	This appears to a well conducted review and it is unlikely that relevant studies were missed; the evidence of increased effectiveness of BLS is based on an observational study rather than an RCT-see section 3.2.2.2 of this report for more details

Review: Velanovich, 1988[41]

Criteria	Comment
Main characteristics:	
Population	Trauma and non-trauma patients (not defined)
Intervention	Any crystalloid
Comparator	Any colloid
Outcomes	Mortality
Date of completion of searches	Not stated
Search strategy (databases used, language restrictions, citation searching, handsearching)	No specific details on search strategy
Types of studies included (RCTs only, observational studies included)	RCTs
Inclusion and exclusion criteria (clearly defined, applied by more than one reviewer)	Clear inclusion criteria (RCTs, studies that differ only in treatment of interest, mortality as outcome) No details on assessment of identified studies
Data extraction (process, performed by more than one reviewer)	No details
Quality assessment (was it performed, what were the criteria)	No quality assessment
Quantity of studies identified	7 studies identified, 4 studies had a the population that consisted solely of trauma patients (n=589 – trauma patients only)
Synthesis of results (were results pooled, was clinical or statistical heterogeneity assessed, sub-group analyses)	Meta-analysis performed for all studies and trauma sub-group; no details on assessment of clinical or statistical heterogeneity
Direction of effect	There was a non significant trend towards crystalloids being more effective in trauma patients
Summary (key findings and validity)	There were few methodological details and it not possible to assess whether the author could potentially have missed relevant studies; there were no details on the study quality, types of crystalloid or colloid, resuscitation protocols, additional interventions or case-mix; it is not possible to conclude whether a specific colloid or crystalloid would of benefit to a particular trauma patient.

Review: Bisonni *et al*, 1991[36]

Criteria	Comment
Main characteristics:	
Population	Injured patients with hypovolaemia; patients with surgical stress; patients with pulmonary failure
Intervention	Any crystalloid
Comparator	Any colloid
Outcomes	Mortality
Date of completion of searches	No details on search strategy
Search strategy (databases used, language restrictions, citation searching, handsearching)	No details on search strategy
Types of studies included (RCTs only, observational studies included)	RCTs
Inclusion and exclusion criteria (clearly defined, applied by more than one reviewer)	No inclusion criteria stated; no details on assessment if identified studies
Data extraction (process, performed by more than one reviewer)	No details on data extraction
Quality assessment (was it performed, what were the criteria)	No quality assessment
Quantity of studies identified	7 studies were identified, 4 related to trauma patients
Synthesis of results (were results pooled, was clinical or statistical heterogeneity assessed, sub-group analyses)	Results were pooled; no assessment of clinical or statistical heterogeneity; sub-group of 4 studies with injured patients with hypovolaemia (n=255) examined separately
Direction of effect	There were no statistically significant differences in mortality between the crystalloid or colloid group
Summary (key findings and validity)	There were few methodological details and it not possible to assess whether the author could potentially have missed relevant studies; there were no details on the study quality, types of crystalloid or colloid, resuscitation protocols, additional interventions or case-mix; it is not possible to conclude whether a specific colloid or crystalloid would of benefit to a particular trauma patient.

Review: Schierhout & Roberts, 1998[40]

Criteria	Comment
Main characteristics:	
Population	Patients with trauma or burns, sepsis or undergoing surgery
Intervention	Any crystalloid
Comparator	Any colloid
Outcomes	Mortality
Date of completion of searches	June 1997
Search strategy (databases used, language restrictions, citation searching, handsearching)	Comprehensive search strategy (several databases, handsearching, checking reference lists, contacting authors; no details on language restriction)
Types of studies included (RCTs only, observational studies included)	RCTs
Inclusion and exclusion criteria (clearly defined, applied by more than one reviewer)	Clear inclusion criteria (RCTs, patients with trauma or burns, sepsis or undergoing surgery, unconfounded studies, which differed only in the treatment of interest, mortality as outcome); inclusion criteria applied by two reviewers to identified abstracts
Data extraction (process, performed by more than one reviewer)	Data extracted in terms of type of participant, type of crystalloid and colloid used, duration of follow-up, mortality at end of follow-up; Double-data abstraction
Quality assessment (was it performed, what were the criteria)	Allocation concealment was assessed
Quantity of studies identified	19 studies met the inclusion criteria, 6 had trauma populations (636 patients)
Synthesis of results (were results pooled, was clinical or statistical heterogeneity assessed, sub-group analyses)	Meta-analysis for all studies and trauma subgroup; no significant statistical heterogeneity identified between studies; no statistical evidence of publication bias (using funnel plots); sub-group analysis for studies with adequate concealment of allocation
Direction of effect	There was a trend towards crystalloids being more effective than colloids for trauma patients (both for studies with and without adequate concealment), although this was not statistically significant
Summary (key findings and validity)	This appears to be a well conducted review; there were differences in the types of colloids and crystalloids administered and it is likely that there will have been differences in resuscitation protocols, additional interventions administered and case mix; no firm conclusion can therefore be drawn regarding the advantages of a specific colloid or crystalloid for a particular trauma patient, although there seems to a trend towards crystalloids being slightly more effective overall.

Review: Choi *et al*, 1999[39]

Criteria	Comment
Main characteristics:	
Population	Adults requiring fluid resuscitation
Intervention	Isotonic crystalloid
Comparator	Any colloid
Outcomes	Mortality, pulmonary oedema, length of hospital stay, physiological parameters
Date of completion of searches	November 1996
Search strategy (databases used, language restrictions, citation searching, handsearching)	Fairly comprehensive search strategy (two databases; reference lists reviewed; no details on language restrictions)
Types of studies included (RCTs only, observational studies included)	RCTs
Inclusion and exclusion criteria (clearly defined, applied by more than one reviewer)	Clear inclusion criteria (RCTs, adults requiring fluid resuscitation, isotonic crystalloid versus colloid, outcomes: mortality, pulmonary oedema, length of hospital stay, physiological parameters); inclusion criteria applied independently by two reviewers to identified abstracts ; reviewers were blinded to the journal, author, publication year, results and discussion
Data extraction (process, performed by more than one reviewer)	Double-data abstraction, data extracted in terms of length of stay and follow-up as well as parameters used for methodological quality
Quality assessment (was it performed, what were the criteria)	Quality assessment performed in duplicate (items assessed: randomisation, blinding, patients selection and description, description of interventions and outcomes; nothing on concealment of allocation or follow-up)
Quantity of studies identified	17 studies met the inclusion criteria, 5 were in trauma patients (n=302)
Synthesis of results (were results pooled, was clinical or statistical heterogeneity assessed, sub-group analyses)	Meta-analyses (combined relative risks, 95% confidence interval) performed for total studies and sub-groups; statistical heterogeneity assessed; a random effects model was used to account for interstudy heterogeneity; sub-group analyses performed for trauma patients and high/low methodological scores
Direction of effect	Significant difference between crystalloids and colloids in the trauma sub-group, favouring crystalloids.
Summary (key findings and validity)	This appears to be a well conducted review; there were some differences in the types of colloids and crystalloids administered and it is likely that there will have been differences in resuscitation protocols, additional interventions administered and case mix (1 of the 5 trauma studies related to thermal injury); although crystalloids performed significantly better overall, interpretation of this should be undertaken with caution; no firm conclusion can be drawn regarding the advantages of a specific colloid or crystalloid for a particular trauma patient

Review: Alderson *et al*, 2003[34]*

Criteria	Comment
Main characteristics:	
Population	Patients with trauma or burns, sepsis or undergoing surgery
Intervention	Any crystalloid
Comparator	Any colloid
Outcomes	Mortality
Date of completion of searches	2000
Search strategy (databases used, language restrictions, citation searching, handsearching)	Comprehensive search strategy (several databases, reference lists checked, authors contacted; no details on language restrictions)
Types of studies included (RCTs only, observational studies included)	Limited to controlled studies with random or quasi-random allocation
Inclusion and exclusion criteria (clearly defined, applied by more than one reviewer)	Inclusion criteria were clearly stated (RCTs or quasi-RCTs, critically ill patients as a result of trauma, burns, sepsis or undergoing surgery; intervention: colloid, comparator: crystalloid); retrieved abstracts were checked by two reviewers
Data extraction (process, performed by more than one reviewer)	Previously included studies double-data extracted (see Schierhout & Roberts, 1998)
Quality assessment (was it performed, what were the criteria)	Allocation concealment, blinding and loss-to follow-up were assessed
Quantity of studies identified	38 studies were identified that reported mortality data
Synthesis of results (were results pooled, was clinical or statistical heterogeneity assessed, sub-group analyses)	Meta-analysis (relative risks, 95% confidence intervals) was performed for sub-groups of fluids; statistical heterogeneity was assessed and a fixed effects model was used; sub-group analysis was performed by type of fluid (rather than type of patients as in previous review), with pooled data including trauma, burns, sepsis patients and those undergoing surgery as well as pre-hospital and hospital fluids
Direction of effect	For meta-analyses of hydroxyethylstarch versus crystalloid, modified gelatin versus crystalloid, dextran versus crystalloid and dextran in hypertonic crystalloid versus isotonic crystalloid there were no statistically significant differences in mortality; for the meta-analysis of albumin or plasma protein fraction versus crystalloids there was a significant difference in mortality favouring colloids (pooled relative risk 1.52; 95% CI 1.08-2.13) when one trial with poor allocation concealment was excluded, there was no significant difference (pooled relative risk 1.34; 95% CI 0.95-1.89) ; there was a trend for crystalloids to be more effective (compared to albumin/PPF, hydroxyethylstarch and dextran) and colloids to be more effective compared to modified gelatin
Summary (key findings and validity)	This appears to be a well conducted review; however, as specified, there was no analysis for trauma patients only; it is also likely that there was heterogeneity between trials in terms of timing of intervention, resuscitation regimens, additional interventions and case-mix; there was a non-significant trend for crystalloids to be more effective (compared to albumin/PPF, hydroxyethylstarch and dextran), however, it is thus not possible to draw conclusions regarding the effectiveness of specific colloids compared to specific crystalloids in a particular trauma patient

*This review is an updated version of Schierhout & Roberts, 1998[40]: results stratified by fluid type rather than injury type as a result of comments on the previous version

Review: Wade *et al*, 1997[42]

Criteria	Comment
Main characteristics:	
Population	Patients with traumatic injury and SBP<100 mmHg
Intervention	250ml hypertonic (7.5%) saline (HS) with or without 6% dextran 70 (HSD)
Comparator	250ml of isotonic crystalloid
Outcomes	Mortality
Date of completion of searches	Not stated
Search strategy (databases used, language restrictions, citation searching, handsearching)	Comprehensive search strategy (several literature searches, contact with researchers/clinicians, review of meeting abstracts and proceedings)
Types of studies included (RCTs only, observational studies included)	RCTs
Inclusion and exclusion criteria (clearly defined, applied by more than one reviewer)	Clear inclusion criteria (250 ml of a 7.5% saline solution, SBP of <100 mmHg associated with traumatic injury, control group with isotonic standard of care, endpoint discharge or 30 day survival); not stated whether in- and exclusion criteria applied by more than one reviewer
Data extraction (process, performed by more than one reviewer)	No details given
Quality assessment (was it performed, what were the criteria)	Assessment of blinding
Quantity of studies identified	8 studies comparing HSD with isotonic crystalloid; 6 studies comparing HS with isotonic crystalloid
Synthesis of results (were results pooled, was clinical or statistical heterogeneity assessed, sub-group analyses)	Fixed effects meta-analysis (odds ratio, 95% confidence interval) performed for both groups; no details on assessment of statistical heterogeneity
Direction of effect	There was no statistically significant difference between HS and isotonic crystalloid regarding mortality; there was no statistically significant difference between HSD and isotonic crystalloid regarding mortality, although there was a slight trend towards HSD being more effective (in 7/8 studies)
Summary (key findings and validity)	This appears to a well-conducted review; there were no significant differences between the fluids regarding mortality, although there was a slight trend towards HSD being more effective; there were some sources of clinical heterogeneity (mode and extent of injuries, timing of fluid administration, i.e. pre-hospital or hospital) although the included populations are more homogenous than in the other reviews; in all cases additional isotonic therapy was given as per centre policy - the effect of this is uncertain; no conclusions can be drawn regarding the effectiveness of a specific fluid in a given trauma patient, although a potentially beneficial effect of HSD in some patients cannot be ruled out

Review: Bunn *et al*, 2003[37]

Criteria	Comment
Main characteristics:	
Population	Patients with trauma, burns or undergoing surgery
Intervention	Hypertonic crystalloid
Comparator	Isotonic crystalloid
Outcomes	Mortality
Date of completion of searches	2001
Search strategy (databases used, language restrictions, citation searching, handsearching)	Fairly comprehensive search strategy (based mainly on Cochrane databases or other Cochrane reviews, reference lists checked; no details on language restrictions)
Types of studies included (RCTs only, observational studies included)	RCTs
Inclusion and exclusion criteria (clearly defined, applied by more than one reviewer)	Inclusion criteria clearly stated (RCTs, hypertonic versus isotonic crystalloid, patients with burns, trauma or surgery; hospital or pre-hospital setting); retrieved abstracts screened by two reviewers
Data extraction (process, performed by more than one reviewer)	Data extracted in terms of allocation concealment, number of randomised patients, types of participants and interventions, number of deaths and disability); independent data extraction by two reviewers
Quality assessment (was it performed, what were the criteria)	Allocation concealment was assessed by two reviewers
Quantity of studies identified	17 trials were identified; 6 of these referred to trauma patients (total of 458 patients)
Synthesis of results (were results pooled, was clinical or statistical heterogeneity assessed, sub-group analyses)	Meta-analysis (pooled relative risks, 95% confidence interval) was performed for sub-groups of patients where there was no evidence of statistical heterogeneity
Direction of effect	There was no statistically significant difference in mortality between hypertonic and isotonic crystalloid (trend towards hypertonic being more beneficial) in trauma patients;
Summary (key findings and validity)	This appears to be a well conducted trial; based on 6 trials in trauma patients, there appears to be no significant difference between hypertonic and isotonic crystalloid; there was clinical heterogeneity between the trials in terms of timing of intervention (pre-hospital and hospital), additional treatments given, case mix; no conclusion can be drawn as to the benefits of one fluid over another for a particular trauma patient.

Review: Alderson *et al*, 2003[35]

Criteria	Comment
Main characteristics:	
Population	Patients with hypovolaemia, burns or hypoalbuminaemia
Intervention	Albumin/plasma protein fraction (PPF)
Comparator	No albumin /PPF or crystalloid
Outcomes	Mortality
Date of completion of searches	November 2001
Search strategy (databases used, language restrictions, citation searching, handsearching)	Comprehensive search strategy (several databases, hand searching, reference lists checked; authors contacted; no language restrictions)
Types of studies included (RCTs only, observational studies included)	RCTs
Inclusion and exclusion criteria (clearly defined, applied by more than one reviewer)	Clear inclusion criteria (RCTs, patients with hypovolaemia, burns or hypoproteinaemia; human albumin or PPF compared to no albumin or PPF or crystalloid; mortality as outcome); inclusion criteria applied by two reviewers
Data extraction (process, performed by more than one reviewer)	Data extracted in terms of study design, allocation concealment, participants, interventions and mortality; double-data extraction
Quality assessment (was it performed, what were the criteria)	Allocation concealment was assessed.
Quantity of studies identified	31 trials were identified; one or more deaths occurred in 25 of these; 18 trials referred to patients with hypovolaemia, deaths occurred in 13 of these; only 3/13 trials had trauma patients (n=89), the others referred mainly to patients undergoing surgery
Synthesis of results (were results pooled, was clinical or statistical heterogeneity assessed, sub-group analyses)	Meta-analyses of relative risks (95% confidence intervals) were performed for patient sub-groups where there was no evidence of statistical heterogeneity; a fixed effects model was used
Direction of effect	For the sub-group with hypovolaemia (with or without studies with adequate concealment) there was a statistically non-significant higher risk of death with albumin
Summary (key findings and validity)	The review appears to have been well conducted, although it appears that studies with fairly heterogeneous patient groups have been pooled; the majority of studies included in the hypovolaemia sub-group are in patients undergoing surgery; within the three studies with trauma patients in this group there are likely to be differences in resuscitation protocols, additional interventions and case mix; no conclusions can be drawn regarding the effectiveness of albumin for a specific type of trauma patient.

Review: Wilkes & Navickis, 2001[43]*

Criteria	Comment
Main characteristics:	
Population	Any patient requiring albumin
Intervention	Albumin
Comparator	No albumin, a lower dose of albumin or crystalloid
Outcomes	Mortality
Date of completion of searches	November 2000
Search strategy (databases used, language restrictions, citation searching, handsearching)	Comprehensive search strategy (several databases, internet search, reference lists checked, authors contacted, no language restrictions)
Types of studies included (RCTs only, observational studies included)	RCTs
Inclusion and exclusion criteria (clearly defined, applied by more than one reviewer)	Clear inclusion criteria (RCTs, albumin versus no albumin, a lower dose of albumin or crystalloid, mortality as outcome); inclusion criteria applied by two reviewers
Data extraction (process, performed by more than one reviewer)	Data extracted in terms of time periods of enrolment, treatment protocol details, patient demographic data and other criteria; double-data extraction
Quality assessment (was it performed, what were the criteria)	Assessment of intention-to-treat analysis and concealment of allocation
Quantity of studies identified	55 relevant trials were identified, deaths occurred in 42 of these; 21 trials referred to surgery or trauma (2 of these referred to trauma patients only)
Synthesis of results (were results pooled, was clinical or statistical heterogeneity assessed, sub-group analyses)	Meta-analysis (pooled relative risk, 95% confidence intervals) was performed using a fixed effects model where no evidence of statistical heterogeneity was found; test for publication bias was performed; sensitivity analyses were performed according to patient sub-groups, quality and trial size; there was no separate sub-group analysis for trauma patients
Direction of effect	There was a non-significant trend for the control to be more effective in surgery and trauma patients; neither of the two trials in trauma patients showed a significant effect in either direction; the authors found evidence of small trial bias, however there was no significant effect if analysis was limited to trials with over 100 patients
Summary (key findings and validity)	This appears to a well conducted review; it is unlikely that relevant studies were missed; only two included trials referred to trauma populations only; there are likely to be differences in case mix, additional interventions and fluid administration protocols; no conclusion can be drawn regarding the effectiveness of albumin versus no albumin/less albumin or crystalloid in trauma patients

* Funding was sought from the Plasma Protein Therapeutics Association and the American Red Cross; these organisations played no role in the design, conduct, interpretation or analysis of the study

Review: Bunn *et al*, 2003[38]

Criteria	Comment
Main characteristics:	
Population	Patients requiring volume replacement or maintenance of colloid osmotic pressure
Intervention	Any colloid
Comparator	Any different class of colloid
Outcomes	Mortality
Date of completion of searches	December 2000
Search strategy (databases used, language restrictions, citation searching, handsearching)	Comprehensive search strategy (several databases, reference list checking, hand searching, manufacturers contacted, no language restrictions)
Types of studies included (RCTs only, observational studies included)	Randomised and quasi-randomised controlled trials
Inclusion and exclusion criteria (clearly defined, applied by more than one reviewer)	Clear inclusion and exclusion criteria (RCTs or quasi-randomised controlled studies, patients requiring volume replacement or maintenance of colloid osmotic pressure, any colloid compared to any other colloid, mortality as outcome); inclusion criteria applied independently by two reviewers
Data extraction (process, performed by more than one reviewer)	Data extracted in terms of method of allocation concealment, number of randomised patients, type of participants and interventions, number of deaths, volume of blood transfused and adverse reactions; double-data extraction was performed
Quality assessment (was it performed, what were the criteria)	Concealment of allocation was assessed
Quantity of studies identified	52 relevant trials were identified, deaths occurred in 31
Synthesis of results (were results pooled, was clinical or statistical heterogeneity assessed, sub-group analyses)	Meta-analyses (pooled relative risk, 95% confidence interval) were performed using a fixed effects model where there was no evidence of statistical heterogeneity; there were no sub-group analyses for patient type - all meta-analyses were conducted by fluid types and contained a mixture of patients with hypovolaemia, trauma, undergoing surgery, with sepsis or other condition
Direction of effect	There was no statistically significant difference between albumin/PPF versus gelatin (1 study), modified gelatin versus hydroxyethyl starch (9 studies), albumin/PPF versus hydroxyethyl starch (11 studies)
Summary (key findings and validity)	This appears to a be a well conducted review; it is unlikely that any relevant studies were missed; no conclusions can be drawn regarding the effectiveness of different colloids in trauma patients as all meta-analyses contained a mixture of patient types; in addition it is likely that fluid administration protocols, additional interventions and case-mix differed between studies with similar patient types

Review: Kwan *et al*, 2003[30]*

Criteria	Comment
Main characteristics:	
Population	Patients with haemorrhagic hypovolaemia of traumatic or non-traumatic origin
Intervention	Any type of intravenous fluids (including blood) - early administration
Comparator	Same type of intravenous fluids - later administration or different volume
Outcomes	Mortality
Date of completion of searches	September 2000
Search strategy (databases used, language restrictions, citation searching, handsearching)	Comprehensive search strategy (several databases, reference lists checked, authors contacted, no language restrictions)
Types of studies included (RCTs only, observational studies included)	Randomised and quasi-randomised controlled trials
Inclusion and exclusion criteria (clearly defined, applied by more than one reviewer)	Clear inclusion and exclusion criteria (patients with haemorrhagic hypovolaemia of traumatic or non-traumatic origin; any type of intravenous fluids-early administration versus same type of intravenous fluids - later administration or different volume; mortality as outcome); a second reviewer assessed a 10% sample of identified studies for in- and exclusion
Data extraction (process, performed by more than one reviewer)	Data extracted in terms of: method of allocation concealment, number of randomised patients, type of participants, interventions, loss-to follow-up and length of follow-up; double-data extraction
Quality assessment (was it performed, what were the criteria)	Assessment of concealment of allocation
Quantity of studies identified	6 relevant studies were identified; 3 related to early versus late fluid administration (1 of which related to blood transfusion); 3 related to different volumes of fluid (1 of which related to blood transfusion)
Synthesis of results (were results pooled, was clinical or statistical heterogeneity assessed, sub-group analyses)	Relative risks (and 95% confidence intervals) were calculated but not pooled due to clinical heterogeneity
Direction of effect	Early versus delayed fluids: there was a statistically significant difference favouring delayed fluids for one study in patients with penetrating injury (Bickell 1994); there were no significant differences in the other two studies (Turner 2000, Blair1986) Different volumes of fluids: there were no significant differences for mortality in the two studies where deaths occurred (Dutton 2000, Dunham 1991); there were some methodological flaws in the studies
Summary (key findings and validity)	This appears to be a well conducted review and it is unlikely that relevant studies were missed; there is some clinical heterogeneity as studies relate to both pre-hospital and hospital settings and there are some methodological flaws in the studies; the authors found no evidence from randomised controlled trials to support the use of early or large volume IV fluid administration in uncontrolled haemorrhage

* an updated version is being prepared for the Cochrane library; the author has kindly made the draft available; no further studies were identified; one trial which is reported as ongoing in the current version now competed (Dutton, 2002[28]); this does not change the conclusions of the review
4/6 identified studies, excluding those relating to blood transfusion, are discussed in detail in this review (Bickell 1994[26], Turner 2000[27], Dunham 1991[29] and Dutton 2002[28]).

Review: Mapstone *et al* (unpublished)[31]

Criteria	Comment
Main characteristics:	
Population	Animals models of uncontrolled haemorrhage
Intervention	Fluid resuscitation (any fluid) - early
Comparator	Fluid resuscitation (same fluid) - delayed or different volume
Outcomes	Mortality
Date of completion of searches	Not stated
Search strategy (databases used, language restrictions, citation searching, handsearching)	Comprehensive search strategy (2 databases, no language restrictions, reference lists checked, authors contacted)
Types of studies included (RCTs only, observational studies included)	RCTs
Inclusion and exclusion criteria (clearly defined, applied by more than one reviewer)	Clear inclusion criteria (RCTs of the timing or volume of fluid resuscitation in an animal model of uncontrolled haemorrhage); inclusion criteria applied independently by two reviewers (disagreements resolved by a third reviewer)
Data extraction (process, performed by more than one reviewer)	Two reviewers independently extracted information on the method of randomisation and allocation concealment, the number of animals in each arm of the trial, the type of animal model, the type of intervention and the associated number of deaths in each group
Quality assessment (was it performed, what were the criteria)	Methods of randomisation and allocation concealment were assessed
Quantity of studies identified	44 studies compared fluid with no fluid resuscitation
Synthesis of results (were results pooled, was clinical or statistical heterogeneity assessed, sub-group analyses)	Meta-analysis (risk ratios, 95% confidence interval) using a random effects model was performed for all studies and for sub-groups (haemorrhage model, reporting of blood loss volume, hypotensive versus normotensive); tests for statistical heterogeneity were performed
Direction of effect	There was no statistically significant difference in mortality according to early or delayed fluids (risk ratio=0.88, 0.73-1.07, trend towards favouring fluids); there was a statistically significant difference in mortality favouring fluids for the aortic injury and >50% tail resection in rats sub-groups, and for studies where blood loss volume was reported; there was a statistically significant difference in mortality favouring no fluids for the <50% tail resection in rats and other vessel injury sub-groups as well as for the sub-group where volume of blood loss was not reported; there was a statistically significant difference in mortality favouring hypotensive resuscitation
Summary (key findings and validity)	This appears to be well conducted review and it is unlikely that relevant studies were missed; there is uncertainty around the relevance of randomisation and allocation concealment for the quality assessment of animal studies (only two studies described how animals were divided into treatment groups); there was a large amount of heterogeneity in the effect of fluid resuscitation on the risk of death, much of which was explained by the type of haemorrhage model used; fluid resuscitation appears to reduce the risk of death in animal models of severe haemorrhage, but increases the risk of death on those with less severe haemorrhage; hypotensive resuscitation reduced the risk of death (based on 9 trials); the results of this study cannot necessarily be extrapolated to humans

Appendix 6 Characteristics of included studies

Table 12 Main characteristics of included studies

Study	Trial design	Population	Intervention	Comparator	Main outcomes	Length of follow-up	No. of participants	Comment
Bickell *et al*, 1994, USA[26]	Parallel RCT	Patients >/=16 years with penetrating injuries (gunshot or stab wound to torso, SPB</=90 mmHg) (retrospective inclusion criteria)	Fluids delayed until surgical intervention	Fluids given before surgical intervention in both pre-hospital (en route) and trauma-centre setting	Mortality before reaching operating room; survival to discharge; post-operative complications; length of stay; laboratory values	Until death or discharge alive	n=598	
Turner *et al*, 2000, UK[27]	Parallel RCT	Trauma patients >/=16 years, who died or stayed in hospital >/=3 days, were admitted to ICU or died within 6 months (majority blunt injury) (retrospective inclusion criteria)	Fluids withheld until arrival at hospital (unless time likely to be above 1 hour)	Fluids given pre-hospital to those patients who would normally receive fluids under current paramedic procedures	Mortality; change in Triage Revised Trauma Score; complications; length of stay; admission to ICU, quality of life	Deaths recorded up to 6 months; health status questionnaire after 6 months	n=1309	Decision whether or not to initiate intervention or comparator remained that of individual paramedic
Dunham *et al*, 1991, USA[29]	Parallel RCT	Patients 14-60 years, direct admission from scene, evidence of hypovolaemia, SBP<90Torr; not stated for whole group whether	Rapid Infusion System™ used (single catheter), resuscitation to same endpoints as comparator; overall more fluids infused	Conventional infusion system (several catheters), resuscitation to same endpoints as intervention; overall less fluid infused within first	Mortality; complications; days in ICU; costs	Cut-off point for recording deaths not stated (at least up to day 6)	n=36	Fluids given on admission to hospital from the scene if patients had hypovolaemia and SBP <90 Torr; not clear whether any pre-hospital fluids;

Study	Trial design	Population	Intervention	Comparator	Main outcomes	Length of follow-up	No. of participants	Comment
		blunt or penetrating injuries	within first hour (less over 24 hours)	hour (more over 24 hours)				compare fluid use during 1st hour and 24 hours, no comparison of fluids infused during period of active bleeding
Dutton *et al*, 2002, USA[28]	Parallel RCT	Patients presenting from scene of traumatic injury, evidence of ongoing haemorrhage, SBP<90mHg; around half with blunt and half with penetrating injuries	Fluid administered to achieve target systolic blood pressure of 70mmHg	Fluid administered to achieve target systolic blood pressure of >100 mmHg	Mortality	Cut-off point for recording deaths not stated (deaths occurred between 0.1 and 8.22 days)	n=110	Assume that more fluids given to achieve higher blood pressure but not actually stated (volumes not detailed) Not clear whether any pre-hospital treatment; study conducted in period of active bleeding between arrival at hospital and end of active bleeding

Table 13 Quality of included studies

Study	**Patient selection and enrolment**	**Randomisation**	**Concealment**	**Loss to follow-up and intention-to-treat analysis**	**Compliance with protocols/crossovers**	**Comparability of groups (baseline criteria, treatment throughout trial, surgical interventions, additional treatment)**	**Other (e.g. follow-up times clearly stated, were different interventions confined to active bleeding period, were there sufficient patients in trial to show effect)**
Bickell *et al*, 1994[26]	Consecutive sample; patients with a Revised Trauma Score of 0 and those with minor injuries subsequently excluded; appears that all eligible patients were included	Patients enrolled into different treatment groups according to 24 hour paramedic shifts on alternate days; unlikely to be a selection bias according to day	Not possible as randomisation was by day, however, it was not possible to influence which arm a given patient will be allocated to	ITT not possible as all patients randomised and inclusion and exclusion criteria applied retrospectively; no loss to follow-up after randomisation	Protocol was adhered to in majority of patients; 22/289 patients in the delayed fluids group transiently received fluids before surgical intervention; fluid was not delayed in any of the immediate resuscitation group	Baseline characteristics similar; not stated if there were any differences in surgical interventions or any differences in interventions between arrival at trauma centre and OR (if any)	Follow-up times clearly stated; different interventions in pre-hospital period only (before surgical intervention)-not clear whether any interventions given between arrival at trauma centre and arrival in OR; power calculation performed
Turner *et al*, 2000[27]	Attempts made to track all eligible patients' report forms (around 5% of potentially eligible not included); minor injuries excluded; not clear if exclusion criteria appropriate	Random number generator used to randomise individual paramedics (later crossed over); stratified by base ambulance station; some imbalance in how many patients randomised to each group in 2nd crossover period	No concealment as cluster randomisation used; not possible to influence which arm a given patient will be allocated to	5% loss to follow-up; ITT not possible as all patients randomised and inclusion and exclusion criteria applied retrospectively; no loss to follow-up after randomisation	Poor compliance with protocols (%): Fluids A B Yes 30.9 20.2 No 69.1 79.8 (A=immediate, B=delayed)	Similar baseline characteristics; Similar amounts of fluids given to both groups in A&E and pre-theatre; no details on surgical interventions	Follow-up times clearly stated; fluids given to similar numbers in both groups in A&E; time period between arrival at hospital and theatre not clear; some patients (around 20%) had more than an hour contact time (on scene and transfer-according to protocol these would have been given fluids regardless of group)

Study	**Patient selection and enrolment**	**Randomisation**	**Concealment**	**Loss to follow-up and intention-to-treat analysis**	**Compliance with protocols/crossovers**	**Comparability of groups (baseline criteria, treatment throughout trial, surgical interventions, additional treatment)**	**Other (e.g. follow-up times clearly stated, were different interventions confined to active bleeding period, were there sufficient patients in trial to show effect)**
Dunham *et al*, 1991[29]	Not clear if all eligible patients were enrolled	No details on randomisation method	No details on concealment	No ITT for overall analysis; can calculate for deaths	No details on compliance or crossover	Some differences in baseline characteristics (ISS); not clear what treatment patients received before arrival at trauma centre; not clear if there was a difference in surgical interventions by group	Different interventions not limited to active bleeding period (more fluids infused during first hour with RIS system, cumulative fluids after 24 hours less); cut-off point for recording death not clear; authors claim that RIS group patients may have been sicker to start with
Dutton *et al*, 2002[28]	Not clear whether all eligible patients included (were enrolled before consent-not clear what happened to those who later declined)	No details on randomisation method	No details on concealment	No details on loss to follow up; not clear whether any patients refused consent	No details on compliance or crossover	Some differences in baseline characteristics (ISS); not clear what treatment patients received before arrival at trauma centre; not clear if there was a difference in surgical interventions by group	Not clear if there was actually a difference in fluids given to different groups-assume that higher blood pressure group got more; cut-off point for recording death not clear

Table 14 Outcomes of included studies

Laboratory findings not listed

Study	Outcome measure	Intervention	Control	Summary measure/p-value	Direction of effect	Comment
Bickell *et al*, 1994, USA[26]		**Delayed fluids**	**Immediate fluids**		Significant reduction in overall mortality and hospital days in the delayed fluids group and trend towards fewer post-operative complications; no difference in mortality before reaching the operating room	
Mortality	Mortality before reaching operating room	29/289	41/309			
	Total mortality (up to death or discharge alive)	86/289	116/309	p=0.04		
Complications	Post-operative complications: patients with>1 complication	55 (23%, 95% CI 18%-29%)	69 (30%, 95% CI 25%-36%)	p=0.08		
Length of stay	Hospital days	11 +/-19	14 +/-24	p=0.006		
	ICU days	7 +/-11	8 +/-16	p=0.30		
Turner *et al*, 2000, UK[27]		**Delayed fluids**	**Immediate fluids**		No significant differences between delayed and immediate fluids groups in terms of mortality, complications, length of stay or quality of life (mental health score significantly better in delayed fluids group)	Crude OR-11 patients excluded as no info on age or ISS; adjusted OR-adjusted for ISS, age and whether patient was unconscious at the scene
Mortality	All cause mortality	60/610	73/699	Crude OR=1.07 (0.73-1.54) Adjusted OR=0.93 (0.58-1.49)		
	Trauma-related mortality	49/610	58/699	Crude OR=1.04 (0.69-1.55) Adjusted OR=0.86 (0.50-1.49)		
	Mortality excluding early deaths (deaths possibly occurring before the arrival of the ambulance)	53/610 (7 early deaths)	63/699 (10 early deaths)	Crude OR=1.04 (0.70-1.53) Adjusted OR=0.97 (0.60-1.59)		
	Mortality excluding late deaths (deaths occurring 3 or more days after the incident)	38/610 (22 late deaths)	41/699 (32 late deaths)	Crude OR=0.95 (0.58-1.49) Adjusted OR=0.74 (0.40-1.38)		
	Mortality excluding early and late deaths	31/610	31/699	Crude OR=0.88 (0.50-1.45) Adjusted OR=0.75 (0.38-1.48)		

Study	Outcome measure	Intervention	Control	Summary measure/p-value	Direction of effect	Comment
Complications	At least 1/8 major complications	46/610	60/699	Adjusted estimated OR=1.15 (0.75-1.77)		
Length of stay	Admission to ICU	113/610	148/699	Adjusted estimated OR=1.18 (0..82-1.69)		
	Length of stay in hospital (mean nights /SD)	7.7 (8.8)	6.4 (7.3)	Adjusted estimated OR, mean (SE)= -1.2 (1.0), p=0.25		
	Total length of stay in hospital (mean nights /SD)	16.6 (21.3)	16.9 (21.1)	Adjusted estimated OR, mean (SE)= -0.1 (0.84), p=0.91		
Quality of life	SF-36 physical functioning (mean/SD)	56.3 (30.5)	53.4 (31.1)	Adjusted estimated OR, mean (SE)= -4.2 (2.6), p=0.10		
	SF-36 social functioning (mean/SD)	62.9 (32.4)	59.2 (32.2)	Adjusted estimated OR, mean (SE)= -3.4 (2.8), p=0.24		
	SF-36 role-physical (mean/SD)	39.2 (42.6)	35.4 (41.1)	Adjusted estimated OR, mean (SE)= -3.7 (3.6), p=0.30		
	SF-36 role-emotional (mean/SD)	64.0 (42.9)	58.1 (44.2)	Adjusted estimated OR, mean (SE)= -4.7 (3.8), p=0.25		
	SF-36 mental health **Error! Not a valid link.**	68.3 (20.2)	62.9 (22.6)	Adjusted estimated OR, mean (SE)= -4.5 (1.8), p=0.02		
	SF-36 energy/vitality **Error! Not a valid link.**	49.2 (22.2)	48.3 (22.7)	Adjusted estimated OR, mean (SE)= -0.56 (1.9), p=0.77		
	SF-36 pain **Error! Not a valid link.**	57.0 (26.4)	56.0 (27.1)	Adjusted estimated OR, mean (SE)= -0.25 (2.3), p=0.91		
	SF-36 general health **Error! Not a valid link.**	63.0 (23.9)	61.2 (22.6)	Adjusted estimated OR, mean (SE)= -0.19 (2.0), p=0.37		
Composite outcomes	Death or complications	96/610	119/699	Adjusted OR (95% CI)=1.02 (0.71-1.47), p=0.93		

Study	Outcome measure	Intervention	Control	Summary measure/p-value	Direction of effect	Comment
	Death or known poor survival (defined as score below 40 in SF 36-only assessed in those who responded to follow-up)	108/610	114/699	Adjusted OR (95% CI)=0.81 (0.58-1.13), p=0.2		
Dunham *et al*, 1991, USA[29]		**Rapid infusion system**	**Conventional infusion system**		No significant differences in mortality; trend towards fewer complications and shorter length of stay in those who survived 12 hours and who received fluid via the Rapid Infusion system	
Mortality	Total deaths	5/16	5/20			
	Acute deaths (up to 12 hours)	5/16	3/20			
	Late deaths (post 12 hours)	0/16	2/20			
Complications- for survivors of first 12 hours only	Adult respiratory distress syndrome	1/11	4/17	p=0.33		
	Infection	6/11	12/17	p=0.38		
	Pneumonia	0/11	6/17	p=0.03		
	Renal insufficiency	1/11	1/17	p=0.74		
Length of stay- for survivors of first 12 hours only	Total length of stay (days)	24.7 +/-13	35.1 +/-25	p=0.17		
Dutton *et al*, 2002, USA[28]		**Resuscitation up to 70mmHg**	**Resuscitation up to 100mmHg**		No difference in mortality.	
Mortality	Total deaths	4/55	4/55			

Appendix 7 Minimum dataset

Taken from http://www.asancep.org.uk/MDSet.htm
ASA/ JRCALC 14/06/99

MINIMUM DATA SET

Form Details

Ambulance Service
Date of Call
Incident Number
Report Form Number

Patient Details

Name
Address
Age
Date of Birth
Sex
GP
Contact
Postcode

Response details

Date
Vehicle call sign
Vehicle home station
Vehicle location at time of call
Type of call
- 999 + MPDS/CBD code
- GP Urgent
- Other

Times
- Call received by AS
- Time passed
- Mobile
- At scene
- At patient
- Left scene
- At Hospital
- Clear

Destination hospital
Hospital department

Incident Details (Link to AMPDS/CBD Codes where possible)

Type
- Work
- Leisure
- Home

Cardiac
- Arrest
- Pain
- Other

Respiratory
- Asthma
- Other

Neurological
- CVA
- Convulsion

Medical
- Diabetes
- Other

DSH
- Overdose
- Injury

GI
- Pain
- Acute Abdomen
- GI Bleed

Obs & Gynae
- Miscarriage
- Ectopic
- Labour
- APH
- Foetal movements
- Delivered
- PPH

Assault
- Blunt
- Penetrating

Fall
- <2m
- >2m

RTA
- Vehicle occupant
- Driver
- front/rear passenger
- Pedestrian
- Motorcycle
- Cycle
- Entrapment and duration
- Ejection
- Fatality
- seatbelt
- head restraint
- air bag
- child restraint
- crash helmet
- alcohol

Drowning

Psychiatric

Burns
- Area%
- Severity

Other
- Time of incident
- location of incident
- history of incident

Significant Past Medical History

Primary Survey

None

Not known

Details
- Signs & Symptoms
- Allergies
- Medication
- PMH
- Last meal
- Events prior to call
- Other

WHERE APPROPRIATE INCLUDE PERTINENT NEGATIVES

Airway
- Clear
- Blocked
- Aspirated

Spine
- Normal
- suspect

Breathing
- Normal
- Absent
- Abnormal

Circulation
- Radial pulse palpable
- capillary refill >2secs

AVPU

Secondary Survey

ABCD's

Summary of injuries & clinical findings
- Nausea
- buccal mucosa
- pallor
- sweating
- fitting

Picture of body outline
- closed#
- open#
- pain
- echymoses
- abrasion
- laceration
- burns
- foreign body

Serial Observations

Pulse
BP
Respiratory rate
Pupil size
Pupil reaction
GCS
TRTS
Oxygen saturation
Peak flow
Blood glucose
Temperature

WHERE APPROPRIATE INCLUDE PERTINENT NEGATIVES

WHERE APPROPRIATE INCLUDE PERTINENT NEGATIVES

Cardiac Care

Witnessed arrest

Resuscitation

Airway & Breathing

by whom

CPR/ALS prior to AS arrival
by whom times/duration

Treatment by AS
BLS
ALS

Monitor
Rhythm strip
ECG

Initial rhythm

Defibrillation
Manual
AED
Bi/Uni-Phasic

Times
Bystander CPR
EMS CPR
first shock
Cannulation
Drugs/fluids
Time respiration returned
Time circulation returned
Time CPR stopped
Time onset of chest pain

Shocks
Initial rhythm
number
size
result (ROSC)

Other cardiac treatment

WHERE APPROPRIATE INCLUDE PERTINENT NEGATIVES

Splints

cervical collar
size
spinal board

Head/chin tilt/lift
Jaw thrust
Oropharyngeal airway
Nasopharyngeal airway
other device
BVMR
pocket mask
LMA/ Combi Tube

Suction

Manual clearance

Intubation
size
by whom
failed attempt
ventilator settings

Oxygen
flow rate
%

Circulation
cannulation
size
site
failed attempt
total volume given

WHERE APPROPRIATE INCLUDE PERTINENT NEGATIVES

Other procedures

cricothyrotomy
needle thoracocentesis
Intraosseous needle

vacuum mattress
traction splint
vacuum splint
box splint
inflatable splint
frac straps
Sam splints
peripheral circulation in tact
RED
Other

Other treatment

Drugs/Fluids
time
dose
route
by whom

WHERE APPROPRIATE INCLUDE PERTINENT NEGATIVES

Condition on arrival

Crew signature

Working diagnosis

Second CBD/AMPDS Code defined by crew
Spontaneous respiration
spontaneous circulation
AVPU/GCS
Dead
Recognised at scene
by whom
confirmed by doctor
name

Hand over

to whom
time
position
signature
Disposition of property

Disclaimer

suitable wording
signature of patient/ responsible adult

Additional Information

WHERE APPROPRIATE INCLUDE PERTINENT NEGATIVES

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