The Bellamy challenge: it’s about time

Geoffrey P Dobson, H L Letson, D Tadaki

ABSTRACT
In 1984, Col. Ronald Bellamy launched a worldwide challenge to develop a new resuscitation fluid to aid survival after catastrophic blood loss on the battlefield. In 1996, after careful compromise among need, cube weight and efficacy, the US military and later coalition forces adopted 6% hetastarch (HES) fluids for early resuscitation. In the intervening years, evidence has amassed indicating that the HES fluids may not be safe, and in June 2013 the US Food and Drug Administration issued a warning that HES solutions should not be used to treat patients with hypovolaemia or the critically ill. We review the unique challenges of early battlefield resuscitation, why the ‘Bellamy challenge’ remains open and discuss a number of forward-looking strategies that may help to solve the problem. The first two pillars of resuscitation that we believe have not been adequately addressed are rescuing and stabilising the heart (and brain) and the vascular system. The ‘ideal’ resuscitation fluid needs to nurture the heart and body slowly back to health, and not ‘shock’ it a second time with unnatural colloids or large volumes of unphysiological saline-based solutions.

THE UNMET NEED
The wars in Afghanistan (2001–present) and Iraq (2003–2009) have resulted in the highest rates of combat casualties for the US and coalition forces since the Vietnam conflict, and deaths from close proximity blast injury patterns are the most common. Catastrophic haemorrhage is responsible for up to 50% of trauma deaths on the battlefield, and up to 20% of these may be salvageable. In the civilian setting, haemorrhage is responsible for 30%–40% of the 5.8 million trauma deaths globally each year, with a third to a half occurring in the pre-hospital environment. Haemorrhagic shock arises from insufficient cardiac output leading to systemic hypotension, widespread tissue hypoperfusion, ischaemia and hypoxia, inflammation and coagulopathy. Its severity will depend upon the volume of blood lost, the duration of shock and on the ability of the heart and body to compensate with the blood remaining in the circulation. Shock is what John Collins Warren aptly called in the late 1800s ‘a momentary pause in the act of death’.

In a 1984 landmark paper, ‘The causes of death in conventional land warfare: implications for combat casualty care research’, Colonel Ronald Bellamy launched a global challenge to develop a new resuscitation fluid to decrease preventable combat death following severe to massive blood loss (Figure 1). Today, despite advances in blood control technologies such as tourniquets and haemostatic bandages, the ‘Bellamy challenge’ remains wide open. Indeed, many of fluids available today, including those solutions containing hetastarch (HES), may negatively impact on the resuscitation outcome by promoting cardiovascular instability, inflammation and coagulopathy, and increase the likelihood of widespread ischaemia, infection and multiple organ failure.

This article is not an in-depth analysis of current resuscitation fluids but rather a general examination of why the Bellamy challenge has remained elusive for 30 years, the clinical reasons why HES was chosen for far forward resuscitation and the evidence amassing against their continued use. Last, we will review the two pillars of resuscitation that we believe have not been adequately addressed in the Bellamy challenge and suggest a number of forward-looking strategies that may help solve the problem. This is an important topic as future conflicts may require longer evacuation times and ultra-small-volume solutions for hypotensive resuscitation to rescue and stabilise the critically wounded.

HES FLUID RESUSCITATION: THE LOGISTIC ADVANTAGES

In contrast to the prolific literature on laboratory haemorrhagic shock research, there is near silence concerning actual clinical investigation of these pharmacologic interventions for shock. At least in terms of the initial management of the trauma victim, nothing much seems to have been added to the time honored principles of controlling haemorrhage and replacing lost blood.

Bellamy

Traditionally, blood has not been available for far forward combat casualty care, and fluids have been used instead. The resuscitation fluid of choice in the current TCCC guidelines is Hextend which contains 6% HES (670/0.7) in lactated Ringers, and the guideline procedure is as follows: If a field combatant suffers significant blood loss, and has a weak or absent palpable peripheral pulse and/or altered mental status (without head injury), the medic should: (1) minimise or eliminate the imminent threat, (2) stop the bleeding and (3) gain intravenous or intrasosseous access and administer 500 mL of Hextend. If there is no response after 30 min, an additional 500 mL is recommended but no more as volumes greater than 10 mL/kg have been linked to coagulopathic bleeding.
The military adoption of Hextend for initial battlefield resuscitation was based on a careful compromise among need, cube weight and efficacy. HES is a colloidal plasma expander and comes in many different molecular weights and molar substitutions. When injected intravenous or intravenous, HES in lactated Ringers draws fluid from the extravascular space into the blood, raises mean arterial pressure (MAP), and generally has a longer intravascular presence than normal saline or lactated Ringers alone. Thus, colloids may be beneficial for delayed evacuation times since 1 L of 6% HES intravascularly is equivalent to about 6 L of lactated Ringers meaning that a field medic could carry less weight with more life-saving potential.

In 2010, the same year the US military endorsed the continued use of Hextend, the world of intravenous fluid management was shaken to read the news that Dr Joachim Boldt, a leading German anaesthesiologist and proponent of HES, was accused of misrepresenting his clinical trial data. On further investigation, Boldt was fired from Klinikum Ludwigshafen and nearly 90 of his referenced publications were retracted from 11 leading journals by a consortium of editors. This development had important military considerations because many of Boldt’s studies formed the basis of clinical guidelines for HES fluid therapy worldwide. During a period of 10 years when Boldt and colleagues were claiming clinical safety and efficacy of HES, an increasing number of animal and clinical studies were showing adverse events including increased risk for bleeding, heart and kidney failure, shock and death. Among the key studies reporting adverse effects of HES is a retrospective analysis of 2225 critically ill trauma patients by Lissauer and colleagues at the University of Maryland Medical Center. The authors concluded that in those patients who received 6% HES there was significantly higher renal dysfunction and death. Béchir and colleagues also cautioned against the use of a second generation 10% HES (HES 200/0.5) in humans, as they found it was associated with fatal outcomes within the first 24 h after severe burn injury. Hartog and colleagues further questioned the use of a third generation HES (Voluven; HES 130/ 0.4) after analysis of 56 randomised trials.

Figure 1 A brief history of small-volume fluid resuscitation for traumatic haemorrhagic shock.

Box 1 The three life-saving ‘windows’ in the Tactical Combat Casualty Care guidelines (see Butler15–17)

- Care under fire’ refers to care rendered at the scene, and is limited to those treatments carried out by the combat medic, and often a surgeon in the case of special operation teams. This window is called the Platinum 5 to 10 min.
- Tactical field care’ is the care rendered once the casualty and/or the unit is no longer under hostile fire or imminent threat. Medical treatment is still limited by time and space and encompasses the Golden Hour.
- Combat casualty evacuation care’ is the care rendered while the casualty is being evacuated which may take a number of hours until more definitive surgical care and triage are available.

1967 WORLD WAR II. Beecher showed benefit of “limited” intravenous infusion volumes to achieve systolic pressure of ~80 mmHg is required.
1929 Cannon introduced the term “hemostasis” as dynamic state of constancy (steady state) despite external changes.
1919 Weig and McIlwraith first used of hypertonic saline (9% NaCl: 30% NaCl) for cerebral edema at The Army Neu-Surgical Laboratory, Baltimore, MD, USA.
1918 WORLD WAR I. Cannon. Crevello argued aggressive intravenous fluid resuscitation led to poor outcomes. They defined shock in a clinical sense, and stressed the importance of keeping systolic pressure low (~80 mmHg) using delayed resuscitation for uncontested blood loss.

RETHINKING THE HES STRATEGY: THE ‘GOOD, BAD AND THE UNKNOWN’

In 2010, the same year the US military endorsed the continued use of Hextend, the world of intravenous fluid management was shaken to read the news that Dr Joachim Boldt, a leading German anaesthesiologist and proponent of HES, was accused of misrepresenting his clinical trial data. On further investigation, Boldt was fired from Klinikum Ludwigshafen and nearly 90 of his referenced publications were retracted from 11 leading journals by a consortium of editors. This development had important military considerations because many of Boldt’s studies formed the basis of clinical guidelines for HES fluid therapy worldwide. During a period of 10 years when Boldt and colleagues were claiming clinical safety and efficacy of HES, an increasing number of animal and clinical studies were showing adverse events including increased risk for bleeding, heart and kidney failure, shock and death. Among the key studies reporting adverse effects of HES is a retrospective analysis of 2225 critically ill trauma patients by Lissauer and colleagues at the University of Maryland Medical Center. The authors concluded that in those patients who received 6% HES there was significantly higher renal dysfunction and death. Béchir and colleagues also cautioned against the use of a second generation 10% HES (HES 200/0.5) in humans, as they found it was associated with fatal outcomes within the first 24 h after severe burn injury. Hartog and colleagues further questioned the use of a third generation HES (Voluven; HES 130/ 0.4) after analysis of 56 randomised trials.
and they concluded that safety has not been adequately addressed. In 2012, Perner et al conducted a 798 patient study comparing the effects of Voluven with Ringers-acetate in sepsis patients and showed that HES was associated with an increase in absolute risk of death (number needed to harm=13). Of military significance, Ogilvie and coworkers examined the effect of 500–1000 mL Hextend on 1714 patients (805 received Hextend), volumes similar to what is currently recommended in the TCCC guidelines and at their Level 1 trauma centre in Florida. The group concluded that initial resuscitation with 6% HES was associated with reduced mortality and no obvious coagulopathy. Unfortunately, there were a number of limitations of this study: (1) the study was not blinded or randomised; (2) the Hextend group had significantly more intensive care unit admissions (41% vs 35%) with a larger number of blood transfusions (34% vs 20%), plasma transfusions (20% vs 12%), and significantly higher rates of septic shock and acute respiratory disease syndrome; and (3) the fluid was administered within 2 h of hospital admission and not immediately on site, as would be mandatory on the battlefield.

On 24 June 2013, after examining the growing number of experimental studies and large randomised trials cautioning HES use, the US Federal Drug Administration issued a ‘box warning’ and concluded that HES solutions should not be used to treat hypovolemic patients, the critically ill (eg, those with sepsis) or those patients undergoing cardiac surgery. In the same month, the European Medicines Agency formally suggested that HES be banned altogether. Whether these new developments will impact on the safety and efficacy of Hextend’s use for initial resuscitation according to the TCCC guidelines on the battlefield remains unknown.

**BATTLEFIELD RESUSCITATION: WHAT ARE WE MISSING?**

While the widespread training of medics in tactical combat casualty care (TCCC) has clearly saved lives, the use of saline and colloid starch by medics on the battlefield does not represent a significant technological advance in ability since saline was first used for resuscitation in 1831.

Blackbourne and colleagues This 2010 pronouncement by key opinion leaders was alarming but not surprising. The resuscitation field (military or civilian) has had little or no evidence-based fluid innovation for over 100 years. Animal models using saline fluids with or without pharmacological ‘adjuncts’ such as calcium-channel blockers, ATP-pathway modifiers, prostaglandins, pyruvate, Na+/H+ exchange inhibitors, pentoxifylline, dihydriopandrostosterone, phosphodiesterase inhibitors or a variety of colloids (HES, dextran-70, gelatins) have all had limited success in translation to humans. However, two adjuncts, valproic acid and 17 beta-oestradiol, have shown a number of promising clinically-relevant attributes, such as cardiovascular support, blunting the inflammatory response and multiple organ protection, and further translational studies are required.

In addition to finding a suitable ‘adjunct’, the other piece of the puzzle is finding a suitable vehicle in which to deliver the drug(s). Both drug(s) and vehicle must be therapeutic and not ‘shock’ the body a second time. In clinical practice, large-volume resuscitation using lactated Ringers or normal saline solutions are commonplace, but smaller volume vehicles such as hypertonic saline solutions may be more beneficial.

Interest in small-volume hypertonic saline solutions began in the 1980s after De Felippe and colleagues showed that 7.5% NaCl (100–400 mL) resuscitated 11 out of 12 patients in terminal hypovolaemic shock after larger volumes of isotonic crystalloids had failed (Figure 1). In 1993, Vassar and colleagues in a multicentre trial showed small volume (250 mL) 7.5% NaCl improved survival of patients but the addition of 6% dextran-70 was of no further benefit in the setting of rapid urban transport. In animal models, 7.5% NaCl has been shown to rapidly expand plasma volume but for longer term ‘pressor’ effect requires a suitable colloidal agent. Hypertonic saline also appears to have positive immunomodulatory properties, improve the microcirculation and oxygen delivery, and significantly reduce intracranial hypertension following traumatic brain injury (TBI). Unfortunately, 7.5% NaCl solution, with or without a colloid, has not translated into clinical practice, although the small-volume hypothesis remains attractive for the concept of permissive hypotension, and with the overall scheme of damage control resuscitation in the pre-hospital setting.

In summary, there is a growing clinical consensus that there should be less emphasis on aggressive larger volume fluid replacement after haemorrhagic shock, as was common in the Vietnam war (Figure 1), and more emphasis on goal-directed, small-volume therapies that nurture the critically wounded slowly back to health, not create more harm. New resuscitation strategies should be developed on the lines of the Chinese proverb: ‘It is better to take many small steps in the right direction than to make a great leap forward only to stumble backward’. Unfortunately, many current fluids may negatively impact on the outcome. Slow restoration of homeostatic balance in the pre-hospital environment requires small volumes and small steps to support the restorative steady-state prior to evacuation.

**WHAT IS THE SOLUTION?**

The properties of an ‘ideal’ fluid for the initial treatment of haemorrhagic shock are summarised in Box 2.

First and foremost, the new fluid should rescue and stabilise the patient immediately on site, as would be mandated in the TCCC guidelines on the battlefield.

**Box 2 A new fluid for far forward battlefield resuscitation should fulfil the following requirements after minimising or eliminating the imminent threat and stopping the bleeding**

- Be easy to administer (intravenous or intraosseous, nano-sized drug delivery).
- Have a low cube weight to maximise benefit to casualty ratio.
- Be stable in different environments.
- Smallest volume possible to rescue the heart and gently raise mean arterial pressure into a permissive range and restore tissue perfusion without causing re-bleeding.
- Prevent secondary brain injury at these hypotensive pressures.
- Blunt the ongoing untoward effects of catecholamines, and possibly the renin system, on cardiovascular, mesenteric (gastrointestinal) and metabolic deterioration to reduce likelihood of organ failure and sepsis.
- Minimise the development of secondary brain injury.
- Reduce whole body O2 metabolism, if possible.
- Slowly restore acid–base balance.
- Blunt the inflammatory cascade.
- Correct acute traumatic coagulopathy.
- Be suitable for burn resuscitation and possibly pain management.

cardiovascular system and neural circuitry within the brainstem to provide sufficient end-organ perfusion for brain, lung and vital organs. The heart is the key target because it is the pressure generator, the vascular system is the pressure (and flow) regulator, and the brainstem is the integrator of both (Figure 2). Outside placing the whole body into a state of therapeutic suspended animation, if the heart and vascular reactivity cannot be rescued, death will be imminent. Surprisingly, there has been limited success in rescuing the heart or brain despite the plea by Shoemaker et al in 1996 for new ways ‘to prevent cardiac arrest during severe haemorrhage before control of bleeding is possible’.64

**FIRST PILLAR OF RESUSCITATION: THE HEART (AND BRAIN)**

Restoration of MAP is lifesaving, but it must be regulated. Regulating MAP via ‘permissive’ hypotensive resuscitation has gained general acceptance on the battlefield.6 The term ‘permissive’ generally refers to the return of a palpable pulse that is required for sufficient reperfusion of the vital organs without dislodging the clot.14 45 50 65 The concept can be traced back to Captain Walter B Cannon and colleagues who, in 1918, suggested the maintenance of a systolic arterial pressure of 70–80 mm Hg to avoid losing more ‘blood that is sorely needed’.51 Cannon’s ‘limited’ fluid approach was later endorsed by Lt Col Henry K Beecher in the Second World War;66 however, it was not widely adopted, and the hypotensive strategy lay dormant for many decades until the early 1980s66–38 47 and the 1994 groundbreaking prospective quasi-randomised trial of Bickell and colleagues50 (Figure 1).

The ‘Bickell’ trial marked the beginning of a sea change in the way hypotensive patients with penetrating truncal injuries were resuscitated, and recommended restricting pre-hospital intravenous fluids to less than 100 mL.50 The most impressive findings of the study were that delayed fluid resuscitation in 289 patents led to fewer days in hospital and less mortality (30% vs 38%) compared with 309 patients who received immediate fluid replacement.49 In 2011, Morrison and colleagues further demonstrated in a prospective, randomised trial that targeting a MAP of 50 mm Hg in the trauma setting, rather than 65 mm Hg, was safe, reduced transfusion requirements and lowered the risk of early coagulopathic bleeding.49 One problem with permissive hypotensive resuscitation, however, is that it is not recommended for TBI,57 and high MAP is not recommended for uncontrolled blood loss. A major innovation in TCCC and pre-hospital civilian resuscitation would be the development of a new small-volume fluid that could resuscitate haemorrhagic shock and treat suspected TBI at the same time. No such fluid exists.

**THE SECOND PILLAR OF RESUSCITATION: VASCULAR ENDOTHELIUM**

Maintaining vascular reactivity is essential to regulate MAP, and minimises regional and global ischaemia–reperfusion injury. An overlooked fact is that within seconds of delivering an intravenous fluid (or any injectable drug), the injected actives are in contact with ~4000–7000 m² of vascular endothelium, the approximate area of a football field68 (Figure 2). This vast endothelial surface, which lies between the blood and the tissues, is a master regulator of vascular tone, inflammation and coagulation, as well as a regulator of mass transport (cells, water, fuels, nutrients and ions), blood fluidity, lymphatic function, and the maintenance and growth of new blood vessels.69

**Preventing loss of vascular tone and cardiovascular collapse**

A longstanding observation in patients who die from traumatic haemorrhage is that the terminal event is marked by a loss of vascular endothelial reactivity or ‘vasoplegia’.70 Vascular function is regulated by central, peripheral and local factors including the sympathetic nervous system, nitric oxide, reactive oxygen species, endothelin and the renin–angiotensin system.70 71 A resuscitation fluid that protects the vascular endothelium may improve clinical outcomes. Since changes in the membrane potential of

---

**Figure 2** The two pillars of far forward resuscitation following severe to catastrophic blood loss are the heart and vascular endothelium. CO, cardiac output; SVR, systemic vascular resistance; MAP, mean arterial pressure.
vascular smooth muscle have been shown to modulate endothelium-dependent relaxation via myo-endothelial gap junctions, a fluid therapy that defends the cell’s voltage around its normal resting potential may also help to prevent cardiovascular collapse. In addition, blood flow-regulating arterioles are innervated by the autonomic nervous system and respond to various stimuli and circulating hormones. Thus, a resuscitation fluid that protects the vasomotor centre located in the brainstem (and higher controls centres) would be imperative for optimal regulation of carotid baroreceptor sensitivity, vascular resistance and multi-organ function.

**Neutrophil–endothelium interactions: function and dysfunction**

A fluid that attenuates the systemic inflammatory response would also be of significant clinical benefit (Box 2). Haemorrhagic shock leads to ischaemia–reperfusion injury, inflammation, coagulopathy, metabolic acidosis, hypothermia, multi-organ dysfunction and, if not treated, death. The inflammatory response occurs from mobilisation and activation of blood borne neutrophils (and other immune cells such as lymphocytes) along post-capillary venules of hypoperfused ‘inflamed’ ischaemic tissues (Figure 3). Upon entry, these killer cells loaded with their toxic weapons are a two-edged sword; they are vital for protecting their toxic weapons are a two-edged sword; they are vital for protecting...
potential assisted by opening KATP channels using adenosine. Theoretically, this strategy would ‘flat-line’ the heart at its resting voltage and confer protection by having fewer channels open, less Na+ and Ca2+ loading, less inflammation, and less arrhythmias during reanimation. What emerged was the world’s first low potassium ‘polarising’ adenosine and lidocaine with Mg2+ (ALM) cardioplegia, which was recently shown to be superior to the standard Buckberg solution in a prospective, randomised trial. The study showed patients receiving ALM cardioplegia had significantly lower troponins, improved postoperative cardiac function, 50% less blood transfusions, one full day less in ICU and two days less in hospital compared with the standard cardioplegia solution.

With respect to decreasing preventable combat or civilian death following severe to massive blood loss, the key point is that ALM at high concentrations arrests the heart, and at lower concentrations resuscitates and protects the heart. In an initial haemorrhagic shock study, the colloids 6% and 10% HES and 6% dextran were shown to promote cardiac instability, compromise haemodynamics and increase mortality during resuscitation in the rat model of severe 40% blood loss. In direct contrast, a second study showed that ~1 mL/kg bolus of 7.5% NaCl–ALM (without colloids) rescued the heart and resuscitated MAP into the hypotensive range with no deaths and the ultra-small volume fully corrected acute traumatic coagulopathy at 60 min. In a third study, there was an unexpected 100% survival in small volume 7.5% NaCl–ALM group following 60% blood loss with improved MAP and few or no arrhythmias compared with 7.5% NaCl alone and other treatment groups. Adenosine-lidocaine also has the advantage of displaying potent anti-inflammatory properties by reducing the priming and activation of neutrophils.

In 2012, Granfeldt and colleagues successfully translated the ALM rat experiments into a pig model of 75% blood loss. A small volume (4 mL/kg 7.5% NaCl–ALM) resuscitated the MAP into the hypotensive region with a twofold increase in stroke volume, a 34% fall in blood lactate and a 43% higher O2 delivery. After the shed blood was returned, whole body O2 consumption fell, systemic vascular resistance increased by 30% and urine output in the ALM group increased threefold compared with 7.5% NaCl treatment. Importantly, small volume 7.5% NaCl alone was not optimal for hypoten
sive resuscitation in rat or pig, which is consistent with the recent randomised, multicentre trial that reported no significant benefit of 250 mL 7.5% NaCl or 7.5% NaCl 6% Dextran-70 compared with normal saline for early resuscitation of haemorrhagic shock (Figure 1). Last, the cardiac rescue potential of small volume 7.5% NaCl–ALM was further demonstrated by Granfeldt et al who showed that a 20 mL bolus of 7.5% NaCl–ALM (0.5 mL/kg) significantly reduced fluid requirement by 40% to reach a target MAP of 50 mm Hg in pig model following 75% blood loss and a 10 mL bolus injection of 0.9% NaCl–AL (no Mg2+) with return of shed blood led to a significant 27% drop in whole body O2 consumption and improved cardiac and renal function.

More recently, ALM rescued the haemodynamics and corrected coagulopathy, including clot retraction, following 8 min of asphyxial hypoxia in rats.

On the battlefield, we envisage a small-volume bolus of hypertonic saline ALM as an initial resuscitation strategy followed by an ALM saline infusion for evacuation; a one–two delivery method for damage control resuscitation. Although the ALM strategy has shown experimental promising results to date, we are mindful of the long list of drugs that have failed to translate into humans after showing compelling superiority in animal models. Further research is required to establish if we have raised the bar to meet the 1984 Bellamy challenge for battlefield resuscitation, and if the innovation represents ‘a significant technological advance in ability since saline was first used for resuscitation in 1831’.

Contributors All authors contributed equally to the planning and writing of the manuscript. GPD takes full responsibility for its overall content and presentation.

Competing interest GPD is the inventor of the ALM technology for cardiac surgery, organ preservation, infection and trauma. GPD currently has no commercial interest in the ALM technology. DT and HL have no conflicts of interest.

Disclaimer The opinions and assertions contained herein are the private views of the authors, and are not to be construed as official or reflecting the views of the US Navy, Military or Department of Defense.

Provenance and peer review Not commissioned; externally peer reviewed.


Received 8 July 2013 Revised 30 August 2013 Accepted 6 September 2013


REFERENCES


8 Wiggers CJ. The Prognostic Significance of Pulse Pressure Changes During Haemorrhage. Arch Int Med 1910;6(Sep):281–92.


13 Letson HL, Dobson GP. Small-volume 7.5% NaCl with 6% Dextran-70 or 6% and 10% Hesetach are associated with arrythmias and death following 60 min of severe haemorrhagic shock in the rat in vivo. J Trauma 2011;70(6):1444–52.


37 Bulger EM. 7.5% Saline and 7.5% Saline/6% Dextran for Hypovolemic Shock. J Trauma 2011;70(Suppl May Supplement):S27–9.


71 Djubur Y, Letson HL, Dobson GP, Adenosine, iododecine and Mg2+ (ALM452) increases survival and corrects coagulopathy after 8 min asphyxial cardiac arrest in the rat. Shock 2013;40:222–32.


The Bellamy challenge: it's about time

Geoffrey P Dobson, H L Letson and D Tadaki

*J R Army Med Corps* 2014 160: 9-15 originally published online October 18, 2013
doi: 10.1136/jramc-2013-000145

Updated information and services can be found at:
http://jramc.bmj.com/content/160/1/9

These include:

**References**
This article cites 88 articles, 3 of which you can access for free at:
http://jramc.bmj.com/content/160/1/9#BIBL

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/