

PRE-HOSPITAL ANTIBIOTIC ADMINISTRATION

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Another Lesson from History?

In our war fighting operations in Iraq and Afghanistan, median pre-hospital transport times are currently 2 hours and 54 minutes. For the T1 casualty (the most critically injured subset) the time from wounding to admission to the Emergency Room is currently 1 hour 40 minutes [1]. We may therefore have made major advances in the care that our soldiers receive when in hospital, but there is still the potential for delay in getting them there. In a recent series from Iraq, 27% of casevaced patients had proven infections. 84% of these were in wounds, but more worryingly 38% had established septicaemias [2]. The ideal way to prevent this infection is early and appropriate surgery, performed by trained and experienced surgeons, in well lit, fully resourced and environmentally controlled hospitals: Such ideals are not always achievable.

One of the greatest medical lessons learned from WW II was the prophylactic use of penicillin in the surgical units closest to the front [3]. By Korea, this had translated into pre-hospital administration by trained medical corpsmen [4]. Sepsis was the major cause of mortality in rear echelon hospitals during the Vietnam conflict, particularly in the setting of extensive burns or penetrating trauma to the head or central nervous system [5]. Our own smaller but more recent experiences have confirmed the value of this pre-emptive approach: In the Field Surgical Teams of the Falklands Campaign, there were no septic limb complications when antibiotics were administered within 3 hours of wounding. Septic wounds resulted in 7 of 9 cases where antibiotic administration was delayed beyond 6 hours [6]. This observation was borne out by later work at Porton Down: Intramuscular administration of Benzylpenicillin, begun within 1 hour of wounding, was effective in preventing streptococcal infections in a pig model of fragment wounds. When this administration was delayed until 6 hours after wounding, the antibiotic was ineffective [7].

The International Committee of the Red Cross has noted that *'All wounded should receive Five Million Units of Penicillin as soon as possible after wounding'* [8]. Our American colleagues have clearly stated that *'Antibiotics should be started as soon as possible after wounding'* [9]. Yet the eminently preventable morbidity associated with open limb wounds still occurs. There was a 15-hour delay to definitive care in Mogadishu [10]. Four out of five of their open fractures of the tibia and both open fractures of the femur became infected: Two thirds of all war wounds are in the extremities [11] yet current UK military pre-hospital care protocols do not

mention forward antibiotic administration by medical personnel in the field. These patients are generally conscious and co-operative. As survivors of military wounds, they are stable and highly unlikely to die in this acute phase from any further bleeding. Is there more that can we do for them?

Current British Army policy is to give iv Benzylpenicillin 1.2g and Flucloxacillin 1.0 g iv (q.i.d) as early as possible and certainly within 6 hours of wounding for limb injuries: Cefuroxime 1.5g and Metronidazole 500mg are given for abdominal wounds [12]. Most commonly, this takes place within a few minutes of arrival in the casualty department of the Field Hospital or FST. When evacuation is delayed, it will not be possible to meet these timelines. Penicillin could be administered further forward, before the casualty has reached the second medical echelon, but there are technical problems. Benzylpenicillin is ambiently heat-stable, but must be given by injection as it is inactivated by gastric acid. Sterile water for reconstitution, needles and syringes are required for its administration. Flucloxacillin is heat and acid stable and can be absorbed by the gut: It remains an important drug for the treatment of uncomplicated staphylococcal infections. However, penicillins can cause allergic reactions, require frequent dosing and are not active against gram-negative organisms.

There are other alternatives and oral fluoroquinolones may provide a solution. Our experience in the UK is mainly with ciprofloxacin but this has poor activity against staphylococci and gram-positive bacteria, as well as requiring twice-daily dosing. Hypersensitivity reactions are rare, even in those with penicillin-allergic reactions [13]. The US military has recently trialled the use of 8-methoxy-fluoroquinolone antibiotics as part of their 'Combat Pill Pack' [14]. This pill pack, now personal issue in combat zones contains 400mg of moxifloxacin, 15mg of meloxicam and 1g of paracetamol. In the event of a combat wound, soldiers are now instructed to take all these pills with just a few sips of water [15]. Originally limited to US Army Rangers and other Special Forces, this pre-hospital use of the combat pill pack is now part of US military doctrine as outlined in their Tactical Combat Casualty Care Handbook [16].

Moxifloxacin is heat-stable and licenced for use in the UK. It is active against gram-negative species - unlike other classical antibiotics it acts against DNA gyrase and topoisomerase IV. It is also active against staphylococcus, streptococcus and clostridia species and has excellent tissue penetration -including CSF [17,18]. It has been proven to be useful orally for abdominal wound and complicated intra-abdominal infections [19]. It has recently been used to treat acinetobacter wound infections from Iraq - although resistance may be becoming a problem. It is very well absorbed orally so, as long as a soldier can swallow, only one 400mg tablet per day is required. A CMT could therefore carry a single strip in their top pocket which

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could treat a whole section for 3 days in the extended (or SF) pre-hospital environment. If a soldier cannot swallow, then pre-loaded needleless ballistic auto-injectors of heat stable dry/liquid antibiotic (currently used in animal models and by the WHO for vaccine administration) remain another distinct therapeutic possibility [20].

There may be no 'magic bullet' for every war wound but is Moxifloxacin 400mg given pre-hospital to wounded soldiers a re-remembered lesson for the British Army?



Figure 1. US Combat Pill Pack.

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PRE-HOSPITAL ANTIBIOTIC ADMINISTRATION: A RESPONSE

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Introduction

The article by Lt Col Parker [1] raises for debate the issue of pre-hospital antibiotic administration and questions current dogma. In order to clearly articulate the rationale for existing policy, it is first important to define the question being debated. The

principle premise is that early severe infections continue to cause death in battle casualties and that this can be reduced by pre-hospital use of novel antimicrobial agents. To review this it is useful to examine the evidence for the incidence of life-threatening early sepsis, identify the microbiological causes, define the predisposing factors, establish the principles and aims of antibiotic use, articulate the constraints on and options for intervention, and finally discuss the evidence supporting any proposed changes to existing policies.

Early, appropriate and repeated surgical intervention has been shown to be crucial in reducing the incidence of subsequent severe infection, and is established as a fundamental principle of War Surgery [2,3,4]. The benefit of early administration of

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antibiotic therapy for established infections, particularly when surgery has been delayed, was established during the Second World War [5]. However in common with many areas of modern medicine, critical evaluation of the evidence that early use of antimicrobials in the pre-hospital environment is independently a significant factor in reduction of morbidity and mortality is lacking.

Wound Infection or Death of the Patient?

Injuries sustained on the battlefield are prone to developing infection for many reasons. These include a breach of skin exposing underlying tissues, implantation of foreign material contaminated with bacteria, tissue damage due to ischaemia and necrosis, penetration of hollow viscera releasing microorganisms into previously sterile areas and delay in surgical intervention. The bacteria associated with battlefield wounds are well documented, but it is important to differentiate between those that cause colonisation or minor wound infection and those that rapidly lead to tissue invasion and severe disease. The potential killer organisms are the pyogenic Gram-positive organisms, *Clostridia* species and some anaerobic streptococci. Perhaps the most important are the organisms of the genus *Clostridium*, including *C. septicum*, *C. novyi*, *C. sordelli* and *C. perfringens* that cause gas gangrene, and *C. tetani* which causes tetanus. Of the Gram positive organisms *Streptococcus pyogenes* is the most significant. *Staphylococcus aureus* is an uncommon cause of early severe sepsis, although there is evidence that this is changing with the appearance of new virulent strains [6]. The anaerobic streptococci are common causes of severe infection, but less frequently recognised by clinicians since the infections are often polymicrobial and seen in association with a wide range of aerobic organisms. Recent studies from the Americans in Iraq and the Russians in Afghanistan confirm these organisms are still found in wounds in the pre-hospital setting [7,8]. Other bacteria may be isolated from the environment and contaminated injuries (notably aerobic Gram-negative rods) but are rarely associated with severe sepsis. They commonly colonise patients without causing disease, particularly those whose normal flora has been suppressed by antimicrobials in the hospital setting [7]. The bacteria causing severe early sepsis are extremely sensitive to antimicrobial agents, including benzyl penicillin. In contrast, the organisms that colonise without causing disease are usually resistant to a variety of drugs, accounting for their selection under antimicrobial pressure and subsequent overgrowth.

Aims of pre-hospital antibiotic administration

In civilian practice trauma victims are usually attended to rapidly by trained paramedics and transferred to hospital for surgery, therefore pre-hospital antibiotics are rarely required. However within the military situation this may not be achievable due to operational constraints in extraction, volume of casualties, patient transfer and evacuation difficulties. It is unrealistic to think that pre-hospital antibiotic administration will prevent wound infection, however it may delay the speed of onset of infection. It is in this situation that antibiotic administration may buy time prior to surgery, preventing wound contamination from becoming serious infection.

When using antibiotics, there are several guiding principles: use the right *drug*, make sure it gets to the right *place*, is there in the right *concentration*, is given for the right *time*, and does not harm the patient.

- a. *Right drug*. If the aim is to prevent life-threatening infection caused by a small number of known pathogens, then the antibiotic should be targeted as accurately as possible. As described above, the bacteria involved are all sensitive to benzyl penicillin and this remains a rational

choice. There is little point using a drug with a wider range of biological activity, since the bacteria killed will include beneficial normal flora in addition to the pathogens. Furthermore widespread use of such broad-spectrum antibiotics rapidly generates antimicrobial resistance with serious consequences. The appearance of clinically significant multi-drug resistant *Acinetobacter baumannii* in US casualties has recently been linked to the use of meropenem and gatifloxacin, when they were given in the pre-hospital setting to prevent wound colonisation by sensitive strains of the same organism [9,10]. In contrast British casualties have generally been colonised with more sensitive organisms reflecting their exposure to different antimicrobials, unless they acquired the bacterium as a result of cross-infection in the US military health care system [11].

- b. *Right place, right concentration*. Killing curves for antimicrobial agents against bacteria mean that most agents must be present at high concentrations where the organism is found. In terms of prophylaxis for infection on the battlefield this means penetrating devitalised tissue with poor blood supply. Theoretically direct local administration of antimicrobials could achieve this, but in practice systemic therapy is given using the highest doses of drug that can be safely achieved. As in the treatment of life-threatening infections in the critical care setting this invariably requires parenteral administration. The pharmacokinetics of drug absorption in a patient whose splanchnic blood supply is diverted elsewhere mean that blood levels are rarely high enough to reach therapeutic levels in tissue, even if the patient is able to ingest oral medication.
- c. *Right time*. The activity of antimicrobial agents is measured in terms of their logarithmic killing of bacteria. It therefore follows that all agents are more effective when there is a smaller bacterial load to be killed. In the context of prophylaxis of battle wounds there is clear logic in achieving therapeutic concentrations in tissue at the earliest possible time, in other words before bacteria have had an opportunity to multiply. Repeated doses are unnecessary for prophylaxis. If timelines are so extended that more than a single dose of any drug is required for what is termed "prophylaxis", then the situation has changed from prophylaxis to therapy of established infection.
- d. *Do no harm*. Clinicians frequently cite penicillin allergy as a reason for modifying their therapeutic approach. In practice allergy is extremely uncommon, with true anaphylaxis occurring in less than 0.05% of patients and serious reactions to penicillins being remarkably rare [12]. In contrast other antimicrobials have common adverse events and complex interactions with other drugs. For example the fluoroquinolone gatifloxacin was withdrawn from the European market following concerns about its hepatotoxicity, whilst moxifloxacin is contraindicated in those who are taking chloroquine, because of the risk of ventricular arrhythmias [13]. The latter interaction is not considered significant in US military personnel since according to their National Guidelines they rarely take chloroquine as malaria chemoprophylaxis on current operations. However for British personnel it would be contraindicated in Afghanistan, or Iraq if the malaria risk were to change again. The alternative would be a complete revision of UK malaria policy. Ciprofloxacin is considered by most practitioners to be relatively safe, but when it has been used for mass chemoprophylaxis for anthrax or meningococcal disease a high proportion of previously healthy individuals complained of adverse events and stopped taking the drug [14, 15].

Current Practice

The basic principles of war surgery are directed at stabilisation and repair of critical structural damage, and removal of foreign material and dead or dying tissue. It is this non-viable tissue that forms the anaerobic environment supportive to the growth of the “killer bacteria”.

Antibiotic use may be divided into three areas; the treatment of established infection post operatively, the peri-operative use of prophylactic antibiotics as in conventional surgery when dealing with high risk procedures or wounds, and the pre-hospital setting. Current UK Military Surgery Guidelines focus on antibiotic use in the hospital setting and recommend that for limb, soft tissue and muscle injuries 1.2g benzyl penicillin should be given on admission, and that cefuroxime and metronidazole should be given peri-operatively when a hollow viscus has been punctured [2]. Treatment of later established infections is usually governed by microbial culture and antibiotic sensitivity testing.

Pre-hospital, the International Committee of the Red Cross recommends benzyl penicillin given within 6 hours [3]. Battlefield Advanced Trauma Life Support states to give antibiotics early when managing military wounds (intravenous or intramuscular) but does not mention a specific antibiotic [16].

The evidence base for pre-hospital antibiotic administration is sparse and often confused in the literature. Most studies have been retrospective, observational, confounded by other factors such as delayed or inappropriate surgery, and they have failed to define clinical outcome measures. None have examined systematically the impact of early antimicrobial use on the incidence of severe sepsis and death. The focus has usually been on wound microbiology alone, but this is clinically irrelevant, generally representing colonisation of resistant organisms in the presence of antimicrobial agents. No studies have been conducted using clinical outcome measures, and there have been very few animal studies. The latter have only considered single species of bacteria in a narrow clinical context, used single species animal models, and therefore the findings cannot be readily extrapolated to the clinical setting in humans. Randomised controlled clinical trials are difficult to organise because of the nature of the trauma, and ethical approval would be difficult to obtain. They are unlikely ever to be conducted. Policy is therefore based on consensus expert opinion, the weakest form of clinical evidence.

The absence of information to guide policy formation also means that it is difficult to assess the efficacy of current practice. There is presently no systematic surveillance of wound infections in British military trauma casualties, which makes subtle variation in clinical outcomes hard to detect. However the key determinants for efficacy of pre-hospital antimicrobial use are severe sepsis and death, which are reported. There have been no cases of either reported in the last 20 years. This suggests that although there have been relatively few trauma casualties until recently, that current practice does in fact achieve its aim and is not a preventable cause of mortality.

Battlefield Considerations

Field constraints dictate that an antibiotic policy in the pre-hospital setting should be simple and pragmatic, involving as few different drugs as possible – ideally a single agent. Logistically drugs should be compact and able to withstand extremes of temperature and humidity. In administration they should be safe, have long half lives, and reliable pharmacokinetics with high blood levels and good deep tissue penetration. This is particularly relevant in situations when drugs are administered by a non-medical officer. Antimicrobials with a narrow spectrum will make subsequent hospital choices simpler and reduce the risk of resistance developing.

At present forward antimicrobials are held by medics rather than individuals. While self- or buddy-buddy administration of analgesia is likely to be undertaken successfully because of immediate perceived benefit to the individuals concerned, it is difficult to envisage that self-administration of antimicrobials will be effective even if they are available. There are examples where self-medication with antimicrobials to prevent the possibility of infection has been advocated but failed due to poor compliance. [17].

Outstanding Questions

There remain a number of unresolved questions.

- Are pre-hospital antibiotics currently given? What drug is actually administered and at what time relative to the injury and subsequent surgery?
- What clinical outcomes are currently evaluated?
- Are current protocols appropriate? How should evidence be produced to evaluate their efficacy?
- How does new information influence changes to practice? Is there a requirement for a formal mechanism to expedite this process?

In late 2007 an active prospective surveillance scheme is being introduced to collect accurate clinical and microbiological information on all battlefield traumatic injuries. It will entail longitudinal follow-up of all such wounds, with regular assessment for clinical evidence of infection and bacteriological examination when indicated. The absence of an existing British Military programme reflects the relative rarity of battle trauma until recently, and the fact that diseases non-battle injury traditionally have, and continue to, form the bulk of casualties. Detailed clinical assessment and defined outcome measures of wound infections will allow accurate analysis to determine the impact of different variables, included amongst them the use of pre-hospital antimicrobial agents. A number of separate research initiatives are also under way to investigate antibiotic use in the battlefield, and the impact of the agents used.

Conclusion

To reduce the risk of death from early and severe wound infection, timely and appropriate surgery is most important. If surgery will be delayed then benzyl penicillin remains the drug of choice, since it is effective against all the “killer bacteria” in this situation and should be given as soon as possible after wounding. The solution suggested by Lt Col Parker is an interesting one that should not be dismissed out of hand. However whilst there may be difficulties with the antimicrobial agents currently available, the idea of early administration of an appropriate antimicrobial agent to an injured soldier is valid. There is danger in making wholesale policy change in the absence of supporting evidence, and the recent US experience is already suggesting what some of the unforeseen consequences may be.

There is no evidence to support a move towards the use of broad-spectrum antimicrobials in the pre-hospital setting to prevent life threatening early sepsis, and accumulating information to suggest that their use leads to an increase in the numbers of patients colonised with multi-drug resistant organisms. Failure to pay attention to scrupulous infection control precautions at all stages of wound management will allow these bacteria to spread to other patients, and lead to complex treatment protocols if late onset infection develops.

Finally more research needs to be done, and better collection and analysis of the information that is already available must be conducted.

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