Antibiotics in Tactical Combat Casualty Care 2002

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Care of casualties in the tactical combat environment should include the use of prophylactic antibiotics for all open wounds. Cefoxitin was the antibiotic recommended in the 1996 article "Tactical Combat Casualty Care in Special Operations." The present authors recommend that oral gatifloxacin should be the antibiotic of choice because of its ease of carriage and administration, excellent spectrum of action, and relatively mild side effect profile. For those casualties unable to take oral antibiotics because of unconsciousness, penetrating abdominal trauma, or shock, cefotetan is recommended because of its longer duration of action than cefoxitin.

Introduction

Infections are an important cause of late morbidity and mortality in combat trauma. The need for early administration of antibiotics was recognized 50 years ago, when Poole[1] stated that "the greatest lesson learned from World War II may have been the benefit of the use of penicillin prophylactically in the surgical units closest to the front." Scott[2] commented after the Korean War that "In any tactical situation where the casualty cannot reach the aid station until 4 or 5 hours or longer after wounding, antibiotic therapy by the aidman in the field is most desirable." 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.[3] Hell[4] states that "a single injection of a broad-spectrum drug with a long half-life should be given prophylactically to personnel on the battlefield to provide bactericidal coverage from the earliest moment after injury occurs." Civilian trauma care also includes the use of prophylactic antibiotics. One standard surgical text notes that "All injured patients undergoing an operation should receive preemptive antibiotic therapy."[5]

Despite these observations and the lessons of past conflicts however, as recently as the 1993 Mogadishu action, antibiotics were not being used by U.S. combat medics.[6] Mabry et al.[6] reported that four of the five open fractures of the tibia from gunshot wounds sustained in this battle became infected. Both open fractures of the femur also became infected. In all, there were 15 wound infections in 58 casualties. Mabry noted that "current U.S. Army doctrine on prehospital care does not call for antibiotic administration by medics in the field." Why has this seemingly simple step in battlefield trauma care been so difficult to implement?

One reason that the military has been slow to adopt the practice of using battlefield antibiotics is that antibiotics are not routinely given in civilian prehospital trauma care. One text notes that "Antibiotics are widely utilized for the prophylaxis of infections in trauma care. It is emphasized that they should be applied early, before an operation is carried out, to be of any use. So far, however, their prehospital use has not been validated."[7] The current edition of the American College of Surgeons-sponsored *Prehospital Trauma Life Support Manual* contains no mention of prehospital antibiotics in civilian care.[8] This practice is quite reasonable given the short transport times to the hospital in most urban trauma centers.

Combat medical personnel who provide prehospital care for their wounded teammates on the battlefield, however, do so under conditions profoundly different from those found in civilian emergency medical systems. The treatment strategies that they use need to take into account the prolonged delays to evacuation commonly encountered in combat operations. There was a 15-hour delay to definitive care for most casualties in Mogadishu.[6] Because of these differences, there has been a renewed call for antibiotics to be included in the care provided by combat medics when there is penetrating abdominal trauma, massive soft tissue damage, a grossly contaminated wound, an open fracture, or when a long delay until Casualty Evacuation is anticipated.[9] In acknowledgment of the differences between the civilian and the military prehospital settings, this recommendation has now been included in the *Prehospital Trauma Life Support Manual* for battlefield trauma, and it is clear that battlefield antibiotics should be added to the care provided by combat medics.[10]

For prophylaxis with antibiotics to be practical and effective, the regimen chosen must be as simple as possible, and the antibiotic should be administered as soon as possible after the injury occurs. The antibiotic coverage has to be maintained at least until surgical debridement has been performed.[4] Coverage must be appropriate for the organisms implicated in combat wound infections. Klein et al.[11] noted that combatants in the Yom Kippur War were treated with penicillin. The most common organism found in wound infections in that conflict was *Pseudomonas*, comprising 25.6% of clinical isolates. Gram-negative bacilli were found to be 70.2% of isolates overall.[11] Mabry et al.[6] also found that *Pseudomonas* and polymicrobial infections were a significant cause of morbidity after the Mogadishu action. Reports from the Russian experience in Afghanistan stated that clostridial species remain an important pathogen on the modern battlefield.[12,13]

The timing of administration is likewise important. Intramuscular benzyl penicillin, begun within 1 hour of wounding, was effective in preventing streptococcal infections in a pig model of fragment wounds. If administration was delayed until 6 hours after wounding, however, the medication was not effective.[14]

Cefoxitin (2 g intravenously) has previously been recommended for battlefield use.[9,10] This drug is an accepted monotherapeutic agent for empiric treatment of abdominal sepsis[15] and provides good coverage for patients with penetrating abdominal trauma.[16,17] Cefoxitin is effective against Gram-positive

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aerobes (except some *Enterococcus* species) and Gram-negative aerobes (except for some *Pseudomonas* species). It also has good activity against anaerobes (including *Bacteroides* and *Clostridium* species).[18] Cefoxitin is supplied as a dry powder, which must be reconstituted by the combat medic with 10 ml of sterile water for injection before administration. It may be given as a slow intravenous push over 3 to 5 minutes.[18] Cefoxitin may also be given intramuscularly if necessary.[18] Additional doses should then be administered at 6-hour intervals until the casualty arrives at a treatment facility.

Gatifloxacin for Oral Antibiotic Prophylaxis

The logistical burden of reconstituting and injecting parenteral medications makes the use of oral antibiotics an attractive alternative if feasible. In some casualties, oral antibiotics are clearly not an option (penetrating abdominal trauma, unconsciousness, shock). In patients without contraindications, however, oral antibiotic prophylaxis is practical and appropriate. The United States Special Operations Command-sponsored workshop on Tactical Management of Urban Warfare Casualties held in Tampa in December 1998 focused on the Battle of Mogadishu and identified a number of potential improvements in the battlefield care of combat casualties. Participants in this workshop noted that an orally administered antibiotic would have several advantages.[19] Giving antibiotics to a wounded teammate would require no more than swallowing a tablet with a sip of water from a canteen and would eliminate the need for mixing and parenteral administration. With a long-acting oral antibiotic, Special Operations (SOF) combat medics could easily carry an adequate supply of antibiotics for several days for the entire unit.

Penicillins are not a good choice in this setting because they: (1) cause too many severe allergic reactions, (2) require too frequent dosing, and (3) are not active against most Gram-negative organisms. The fluoroquinolones, on the other hand, have an excellent spectrum of antibacterial action. Ciprofloxacin has good coverage against *Pseudomonas* species[20] but little activity against anaerobes.[20,21] Levofloxacin has more action against Gram-positive organisms than ciprofloxacin, but it is less effective against *Pseudomonas* and is also not reliably effective against anaerobes. Levofloxacin has some activity against *Pseudomonas* and is indicated for urinary tract infections caused by this organism.[22] Trovafloxacin is effective against Gram-positive, Gram-negative, and anaerobic organisms.[20] Moxifloxacin and gatifloxacin are also fourth-generation fluoroquinolones that have an enhanced spectrum of activity. Trovafloxacin, gatifloxacin, and moxifloxacin yield low minimum inhibitory concentrations against most groups of anaerobes.[21,23] One study found that moxifloxacin activity against *Clostridium* and *Bacteroides* species was in the same range as metronidazole and superior to that of clindamycin.[24] Another study found that "In general, moxifloxacin was the most potent fluoroquinolone for Gram-positive bacteria while ciprofloxacin, moxifloxacin, gatifloxacin, and levofloxacin demonstrated equivalent potency to Gram-negative bacteria."[25] A third study found that moxifloxacin was almost as active as trovafloxacin, as active as gatifloxacin, and more active than levofloxacin and ciprofloxacin against the anaerobes tested (including *Clostridium* species).[26] Blood levels of the fluoroquinolones achieved with oral dosing are similar to those achieved with intravenous dosing; therefore, oral administration does not significantly reduce the bioavailablity of these agents.

Fourth-generation fluoroquinolones have an additional benefit in SOF casualties. Because SOF operations often entail immersion in sea or fresh water, infections with pathogens found in these environments must be considered as well. Wounds contaminated with seawater are susceptible to infections with *Vibrio* species, Gram-negative rods that can result in an overwhelming Gram-negative sepsis with a 50% mortality rate.[27] Contamination of wounds with fresh water may result in infections with *Aeromonas* species, also a Gram-negative rod.[27] The excellent Gram-negative coverage of fourth-generation fluoroquinolones make them good choices in these circumstances.

In addition to the ease and the logistical advantages of oral administration, the fluoroquinolones require less frequent dosing. Both moxifloxacin and gatifloxacin are given as a single daily 400-mg dose. Imagine a SOF team with three seriously wounded individuals that cannot be extracted for 48 hours. To maintain antibiotic coverage with cefoxitin (as previously recommended) for all three casualties would require 24 parenteral doses–a quantity that SOF corpsmen and medics are not likely to carry. In contrast, six tablets of one of the fluoroquinolones would suffice for the same period.

In contrast to the penicillins and the sulfa-based antibiotics, the fluoroquinolones also have an excellent safety profile. A review in the October 1999 Mayo Clinic Proceedings stated that they are tolerated as well or better than any other class of antibacterial agents.[20] The best known toxic effect of the fluoroquinolones has been the severe hepatotoxicity seen with trovafloxacin, but this was seen in only 140 patients of 2.5 million prescriptions and was usually seen after long-term (more than 28 days) use of the medication.[20] Another disadvantage of trovafloxacin is that its absorption is delayed by morphine, which will often be used on combat casualties. Gastrointestinal upset is seen in approximately 5% of patients treated with fluoroquinolones, and mild allergic reactions (rash, urticaria, and photosensitivity) are seen in 1% to 2% of patients. Mild central nervous system symptoms (headache and dizziness) are also encountered in 5% to 10% of patients treated with the fluoroquinolones.[20]

Based on the discussion above, either moxifloxacin or gatifloxacin would be a good choice for an oral antibiotic to use on the battlefield. A cost comparison of these two agents performed by the Naval Hospital Pensacola pharmacy in August 2002 found that the cost to the U.S. government for a single dose of moxifloxacin was $5.09, whereas a single dose of gatifloxacin was only $1.86. This cost comparison is based on the Department of Defense-wide pricing schedules. Based on the much lower cost of gatifloxacin with other factors being approximately equal, gatifloxacin emerges as the best choice for an oral antibiotic. Use of an oral antibiotic means that gatifloxacin can be carried by individual combatants, if they have been trained in its use, and self-administered in the event of penetrating trauma.

One of the considerations in a medication chosen for use by ground troops in the field is its ability to maintain its activity in hot and cold environments. The recommended storage temperature for gatifloxacin is 25°C with 15°C to 30°C listed as the acceptable temperature range.[18] If true, this would limit the

drug's usefulness to ground combat troops. Correspondence on this issue with the manufacturer, Bristol-Myers Squibb, has indicated that gatifloxacin tablets packaged in polyvinyl chloride/polyvinylidene chloride blisters have excellent stability at a wider range of ambient temperatures with documented maintenance of efficacy for 260 weeks at temperatures of 30°C and lower. Efficacy was maintained for 56 weeks at 40°C/75% relative humidity and for 27 weeks at 50°C (P. Carpenter, J. Bergum, Bristol-Myers Squibb, unbpublished data).

Gatifloxacin is a good choice for single-agent therapy based on its excellent spectrum of coverage, good safety profile, and once-a-day dosing. Moxifloxacin would be an acceptable second choice. A third choice might be levofloxacin, but because levofloxacin has only limited activity against anaerobes, another drug must be added to achieve coverage against these organisms. The most active drugs for the treatment of anaerobic infections are clindamycin and metronidazole.[28] Relatively few anaerobes are resistant to clindamycin and few, if any, are resistant to metronidazole.[28] Metronidazole has the additional advantage of having a less severe side effect profile than clindamycin.

Cefotetan Instead of Cefoxitin When Parenteral Antibiotics Are Needed

There are some casualties in whom the use of oral antibiotics is not advisable. An unconscious casualty is not able to take the medication. An individual in shock will have a reduced mesenteric blood flow that might interfere with absorption of an oral agent. Casualties with penetrating abdominal trauma may have a mechanical disruption of the gastrointestinal tract that would impede absorption of an oral antibiotic. Effective antibiotic prophylaxis is especially important in this group of patients. One study of 338 patients with penetrating trauma to the abdomen were reported by Dellinger et al.[29] Even in this civilian trauma center setting, 24% of patients developed wound infections, and nine died as a result.

Use of cefotetan as an alternative to cefoxitin as a battlefield antibiotic was first proposed by O'Connor.[30] Cefotetan is a similar medication with the same broad spectrum of action, but with a longer half-life that allows every 12-hour dosing. Both cefoxitin and cefotetan were recommended by Osmon[31] as prophylactic agents for adults undergoing colorectal surgery and by Conte[32] for trauma victims with a ruptured viscus.

A meta-analysis on antibiotic prophylaxis in penetrating trauma was published by Luchette et al.[33] in 2000. The more successful regimens included: cefoxitin, gentamicin with clindamycin, tobramycin with clindamycin, cefotetan, cefamandole, aztreonam, and gentamicin alone. Nichols et al.[34] compared cefoxitin to a gentamicin/clindamicin combination in penetrating abdominal trauma and found them to be equivalent. Jones et al.[35] compared cefoxitin, cefamandol, and a tobramycin/clindamycin combination in patients with penetrating colon trauma. They concluded that both cefoxitin and the tobramycin/clindamycin combination were superior to cefamandole. In 1992, Fabian et al.[36] compared cefoxitin with cefotetan directly. This study included 515 patients, and they found no difference in efficacy between the two agents.

Whereas cefoxitin and cefotetan appear to be equal in efficacy, the longer half-life and comparable cost make cefotetan a better choice for use by combat corpsmen and medics. Cefoxitin remains a viable alternative and a good second choice. With both choices, dry powders must be reconstituted manually with appropriate diluents. Packaging that allowed for streamlined handling in tactical environments would represent an invaluable advance in the military application of these products. Current recommendations for storage of cefotetan in the powder form are that the vials not be stored at temperatures above 22°C (72°F) and that they be protected from light.[18] Expanded storage and handling guidelines for use in the field should be addressed with the manufacturer should this agent be chosen for use by combat medical personnel.

Antibiotics may be useful to prevent the development of wound infections, but there is no guarantee that they will be effective in all casualties. Wound infection is a function of the number and type of contaminating organisms, the amount of devitalized tissue, the presence of foreign bodies in the wound, and the delay to surgical care. Wounds with large quantities of organisms, foreign bodies, or dead tissue may become infected despite the early use of antibiotics. The use of antibiotics for combat trauma does not lessen the importance of timely surgical treatment of the wound, and there should be no decreased emphasis on the need to obtain definitive care as soon as feasible. In the event of a prolonged delay in evacuation, antibiotic use should be continued until the casualty reaches a medical treatment facility.

The widespread use of a particular antibiotic eventually produces organisms that have developed a resistance to it. It is common practice to use antibiotics for a variety of minor upper respiratory infections, and these infections are common in deployed troops. Should these recommendations be implemented by the military, the importance of avoiding the use of gatifloxacin for the treatment of minor infections in deployed troops should be emphasized to decrease the development of resistant organisms.

Conclusion

We propose that prophylactic antibiotics be used by combat medical personnel for all open combat wounds. Where there is no contraindication to the use of oral antibiotics, (1) gatifloxacin, 400 mg, by mouth once a day and (2) if unable to take oral medications (shock, unconscious, or penetrating abdominal injury), cefotetan, 2 g, intravenously (slow push over 3–5 minutes) or intramuscularly every 12 hours.

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