

## Pretrauma Interventions in Force Health Protection *Introducing the “Left of Bang” Paradigm*

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### Introduction

The delivery of timely and effective emergency trauma care for battlefield casualties is paramount in the business of saving lives during armed conflict. The traditional paradigm for medical care of the war wounded has been a sequence of events on a linear timeline from first responder care at point of injury, moving toward evacuation, onward to medical care, and eventual treatment and rehabilitation in the patient’s home nation. With few deviations, this schedule has been in practice since Napoleonic times.<sup>1</sup> This conventional timescale can be visualized on an axis moving from left to right, often starting from the injury—the “bang.” The military metaphor “left of bang” has been coined to describe the events preceding this point.<sup>2,3</sup> but has not previously been applied to the medical setting.

Historically, the “golden hour”<sup>4</sup> and “platinum 10 minutes”<sup>5</sup> concepts have been applied to postinjury military and civilian trauma care. More recently, this framework has evolved into the Tactical Combat Casualty Care (TCCC) continuum. TCCC is a more nuanced approach that takes into account additional factors including the level of hostile threat and evacuation timelines. The application of this model of trauma care in recent conflicts has led to such a progressive improvement of care for the combat casualty as to be unrecognizable from previous times.<sup>6</sup>

In our search for further improvement in trauma outcomes, we ask the following question: is it now time to explore the concept of trauma care “left of the bang”? Such a movement of attention to a point before battlefield injury would be in keeping with other fields of preventive medicine.

For this perspective article, left of bang innovations in trauma (LOB-IT) are defined as any medical, pharmacologic, or surgical intervention that is delivered before trauma and may act to reduce morbidity and mortality after injury. This review aims to explore potential

avenues for LOB-IT to promote further discussion among the military medical community.

### Historical Context

Preventive practices in nontrauma medical fields have been used in the deployment of military forces. Force health protection is now considered an essential component of battlefield medicine.<sup>7</sup> Field Marshal Rommel’s campaign in North Africa during the Second World War was severely hampered by widespread disease among his troops and generals, including his own staff. Indeed, he was evacuated with hepatitis during the campaign. Meanwhile, General Slim, the Allied Commander at the time, was facing an enormous malaria problem that required prophylactic treatment to maintain a fighting force. Closer to the present day, those involved in the first Gulf Conflict were given pyridostigmine bromide as a prophylaxis against the effects of nerve agent attack, and malaria prophylaxis continues to be paramount for troops deployed to endemic regions (e.g., the recent deployment to Sierra Leone).<sup>8</sup> More recent advances in ballistic protection (individual and collective), as well as vehicle design, have been instrumental in improving survival of trauma casualties.

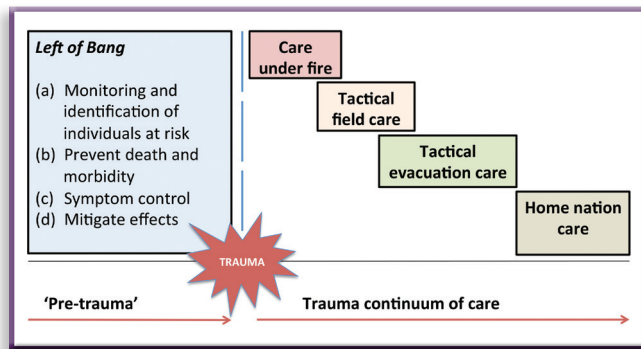
It is in the context of medical force protection that we can now start to explore the LOB paradigm: can some interventions mitigate the effects of injury and prevent death from trauma before it happens?

### Exploring the Paradigm

To explore which innovations and technologies might be used, it is worthwhile discussing what makes an ideal intervention in this context. First, interventions need to cause no harm, a lesson learned from the controversial legacy of Gulf war prophylaxis.<sup>9,10</sup> They must also provide clinical benefit to the potential casualty if they are injured, without hindering the postinjury resuscitation. A favorable cost-benefit analysis may also be relevant

when such measures are implemented across large populations of deployed troops. LOB-IT candidates must also be specifically tailored to level of risk. Relative probability of injury is both personnel and mission specific, and such calculations are already commonplace in the planning of deliberate operations by military commanders. LOB-IT candidates, therefore, may be stratified according to their relative assessment of benefit according to specific tasks and risks. Special Forces personnel would be some of the most likely to benefit from such interventions because of the high-risk environment in which they operate and challenges in accessing timely medical care. Conceptually, there are four ways in which an LOB-IT candidate modality might contribute to advancing trauma care (Figure 1): (a) monitoring and identification of individuals at risk; (b) prevention of death and morbidity; (c) symptom control; and (d) mitigation of effects.

**Figure 1** Schematic representation of how “left of bang” trauma interventions fit into the medical treatment of major trauma patients.



### Nutritional preconditioning

Nutritional optimization for strength and endurance is already relatively commonplace among modern military units. However, such an approach may be pushed further by adopting a more injury prevention-centric model. The benefits of muscle mass, strength, and aerobic and anaerobic power may be increased by protein supplements,<sup>11</sup> and oral carbohydrates taken before trauma and hemorrhage may also provide a survival benefit.<sup>12</sup> Particular attention to weight and body mass index may also be required because of its effects on coagulation after traumatic injury.<sup>13</sup>

In terms of pharmacologic interventions, nutritional supplements could theoretically minimize trauma-related sarcopenia in critically ill trauma patients, with potential survival benefit mediated through, for example, improved ventilator function. The leucine metabolite  $\beta$ -hydroxy- $\beta$ -methylbutyrate has been shown to be a highly promising LOB-IT candidate because of its ability to reduce the incidence of systemic inflammatory response in trauma patients.<sup>14</sup> This agent would be particularly attractive to the uninjured military population

because it has also been shown to augment muscle mass and strength<sup>15</sup> and inhibit exercise-induced muscle damage.<sup>16</sup> Nutritional strategies could also be implemented to improve immune function “in the field.”<sup>17</sup>

### Physiologic preconditioning

The general principle for physiologic preconditioning would be to increase the physiologic reserve and cardiovascular reactivity for optimum response to injury, hemorrhage, and subsequent hypovolemia and acidosis. Outcomes for critically ill trauma patients are worse when they are smokers<sup>18</sup>; therefore, a useful pretrauma intervention would be targeted smoking cessation. Preclinical experiments have shown that exercise preconditioning may protect against the effects of traumatic injury.<sup>19–21</sup> Furthermore, some authors have tested hemorrhagic preconditioning by bleeding animals before a hemorrhagic shock insult, and reported improved vascular reactivity.<sup>22</sup> Erythropoietin treatment may mitigate the organ injury and dysfunction secondary to hemorrhagic shock.<sup>23</sup>

### Coagulation preconditioning

In one recent study of combat deaths, 91% of “potential survivors” were shown to have died secondary to uncontrolled hemorrhage.<sup>24</sup> Thus, prevention of catastrophic hemorrhage would be a crucial area to focus on to improve survival. Tranexamic acid has recently received a lot of attention as a safe and effective drug to mitigate the effects of hemorrhagic shock, including in a prehospital context.<sup>25</sup> It has been reported to have no serious adverse effects in this setting<sup>26</sup> and there is a benefit from early administration.<sup>27</sup> Its use has shifted from only trauma to perioperative use, reducing blood loss and requirement for transfusion.<sup>28</sup> The high potential gain, low risk, and time-dependent benefits of tranexamic acid make this an interesting potential LOB-IT candidate.

### Antibiotic release after injury

Antibiotics are given routinely before infection-prone surgical procedures<sup>29</sup> and, therefore, may be of use after trauma that requires surgical management. However, the prolonged use of prophylactic antibiotics is fraught with the obvious problem of causing harmful antibiotic resistance. Furthermore, the time window of effectiveness of presurgery administration of antibiotics is relatively short,<sup>30</sup> so their use as LOB-IT candidates may be limited. However, it is conceivable that antibiotic release from a pre-implanted device may be triggered after traumatic injury or remotely by medical team activation. Such a speculative notion may not be entirely within the realms of science fiction.

### Symptom Control

There is significant precedent in the area of preemptive analgesia in relation to planned surgery.<sup>31</sup> Trauma is

unplanned, however, and pain secondary to major trauma is challenging to control and incompletely understood. Although some patients report no pain after even the most severe injuries,<sup>32</sup> others experience pain that cannot be controlled by any means. Part of the problem is that after major trauma, peripheral or oral absorption of analgesia is limited by peripheral and gut hypoperfusion secondary to hypovolemic shock. Analgesia is unlikely to provide a favorable risk-benefit ratio when delivered before injury, given the side-effects: opiates have potential to cause cognitive impairment, addiction, tolerance, and respiratory depression. Non-steroidal anti-inflammatory drugs predispose to renal injury, gastric bleeding, impairment of fracture healing, and, possibly, intracranial hemorrhage after head injury.<sup>33</sup> However, analgesia that is already surgically implanted or ready to deploy as described may be a potential LOB-IT candidate.

#### *Physiological Monitoring*

Wearable clothing that provides continuous monitoring of physiology is already available.<sup>34</sup> This technology allows remote monitoring (e.g., from a military medical facility), and may provide immediate, real-time data after injury of a casualty. Applying this technology to combatants before injury has an advantage over conventional monitoring because it is immediate (providing data before, during, and after injury), and can be accessed by medical providers on scene and remotely at any medical facility in the chain of evacuation. Such data provide an obvious advantage in the treatment of traumatic injury through the goal-directed guidance of interventions such as fluid resuscitation.

#### *Mitigation of Secondary Effects of Trauma*

In addition to the acute effects mentioned, there may be a role for LOB-IT candidate treatments in the prevention of early morbidity and mortality after trauma. For example, experimental studies have shown that pretreatment with curcumin can mitigate secondary brain injury in rodent models of head injury.<sup>35,36</sup> This “remarkably non-toxic”<sup>37</sup> agent could be given to those who were a high risk of receiving a head injury. Furthermore, there is some evidence that statins administered before injury may reduce mortality and infection after general trauma and traumatic brain injury, giving it a place as a hypothetical LOB-IT drug.<sup>38</sup>

#### *Mitigation of Psychological Effects of Trauma*

Massive lower limb and pelvic trauma has been a signature injury pattern during the recent conflicts in Afghanistan and Iraq. As well as the obvious consequences of disfigurement, loss of physical functional, and long-term rehabilitation, the important psychosocial consequences of loss of sexual and reproductive function have profound effects on veterans’ well-being. Prior semen

cryopreservation may help mitigate reproductive limitations after traumatic loss of testicular tissue and has been used by military personnel.<sup>39</sup> Although conferring no survival benefit to the individual, the knowledge that sperm had been preserved before injury may contribute to morale and be protective against psychological morbidity postinjury.

#### **Discussion**

As long as human combatants are required to engage in armed conflict, the unfortunate and tragic consequence of violence, injury, and death will follow. Preparedness for traumatic injury and mitigation of its effects as early as possible has been the focus of attention recently. However, rather than focus on “early” care, here we propose that the timeline of trauma care be shifted leftward to a point before injury has even occurred.

#### *Evidence Base*

Generating the evidence base to support LOB interventions in trauma will be challenging because military campaigns may be sudden, impossible to predict, and resources for medical research may be sparse. Many of the potential LOB-IT candidates would be suitable for testing using animal models of battlefield injury. However, there are obvious translatability issues with such preclinical studies, and robust clinical data would be required if animal studies showed some avenues of promise. High-quality medical research in the military and civilian trauma environments is not impossible and has been instrumental in driving practice change. A key example is the use of tranexamic acid in hemorrhage (e.g., the CRASH-2 [Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage] trial).<sup>27</sup>

#### *Ethical Considerations and Risk Stratification*

Trauma, although devastating, is relatively rare among the majority of troops and, therefore, risk stratification would be crucial in deciding who should and should not receive LOB-IT treatments. Furthermore, experience has shown that compliance with prophylaxis among troops may be poor, especially when the risk is perceived as low and the adverse events high.<sup>40,41</sup> In military campaigns, the population at risk for exposure to major trauma will vary depending on multiple factors, including the phase of the campaign, role of the personnel, and evolution of threats. For example, Airborne Forces undertaking a parachute insertion onto enemy-held rocky terrain at night will be more likely to be exposed to major trauma than will support staff in a clerical role in headquarters. The decision as to which population should receive trauma prophylaxis, and which should not, would depend on knowledge of the adverse effects of the medical treatment and a prediction of the risk for exposure to trauma. In addition to risk stratification, the autonomy

of the individual needs to be balanced with the needs of the larger group. The concept of herd immunity cannot be applied to trauma, but there are implications for resource distribution if individuals chose not to be protected as well as they could be. A hypothetical example might be an instance when a Soldier, who chose not to accept a LOB-IT, became injured. The Soldier's potential increased vulnerability may hypothetically increase resource requirement, logistic burden, and danger for the remaining uninjured personnel.

## Conclusion

Efficacious early care following combat trauma has traditionally focused on earlier and speedier care after injury. To push this boundary even further, a LOB paradigm shift is proposed. Such interventions would aim to prevent morbidity and mortality, control symptoms, and mitigate the secondary effects of trauma through the judicious application of medical interventions before traumatic injury has occurred. This proposal has major challenges to overcome if it is to be given full consideration, including the establishment of a robust evidence base, ethical discussion and consensus, and cost-benefit analysis. We propose that it is time to look "left of the bang" and examine what pretraumatic medical treatments can offer.

## Disclaimer

This work is the opinion of the authors and does not represent official policy or research strategy of the UK Defence Medical Services. The ideas discussed herein are speculative and it is our intention to stimulate discussion and to expand the conceptual framework within which trauma care is considered rather than provide fully evidence-based and tested clinical options.

## Disclosures

The authors have nothing to disclose.

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