Difficult Decisions in Surgery:
An Evidence-Based Approach

Kenneth Wilson
Selwyn O. Rogers *Editors*

Difficult Decisions in Trauma Surgery

An Evidence-Based Approach

Springer

Difficult Decisions in Surgery: An Evidence-Based Approach

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The complexity of decision making in any kind of surgery is growing exponentially. As new technology is introduced, physicians from nonsurgical specialties offer alternative and competing therapies for what was once the exclusive province of the surgeon. In addition, there is increasing knowledge regarding the efficacy of traditional surgical therapies. How to select among these varied and complex approaches is becoming increasingly difficult. These multi-authored books will contain brief chapters, each of which will be devoted to one or two specific questions or decisions that are difficult or controversial. They are intended as current and timely reference sources for practicing surgeons, surgeons in training, and educators that describe the recommended ideal approach, rather than customary care, in selected clinical situations.

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This book is dedicated to the community advocates living in the Southside of Chicago and their grassroot efforts that re-opened the trauma center at the University of Chicago after a 30-year absence. Their unyielding advocacy for fixing broken physiology locally is paramount in creating this international trauma text edited at The University of Chicago.

Preface

In the expiring seconds of an adrenaline-charged competition, the "last shot" is entrusted to the individual with unwavering poise, unperturbed by the gravity of the situation. The correct decision needs to be made when the count on the shot clock is unfavorable. In a similar manner, trauma surgeons are men and women with the same strength of character committed to taking and making the last shot even when competing against death. In the case of the trauma surgeon, the consequence of not being focused in the moment can have dire consequences if stuck entertaining vacillating thoughts as the team lead. Quick and resolute decision-making wins the game.

The unfortunate advent of war over many centuries has produced innumerable injury patterns requiring swift surgical decision-making for bleeding cessation. War-time surgeons over the last century and into the modern era, under compulsion, have improved trauma care by critically evaluating dilemmas and forcing refinements. Innovations in vascular injury management, patient transport, advancements in antibiotics and field resuscitations, all mastered by intrepid surgeons, have considerably impacted how trauma care is delivered today. Civilian clinical decision-making has also been considerably advanced by the conundrum of complex injury patterns experienced by trauma surgeons. In both military and civilian sectors, the trauma surgeon stands often as the last line of defense between severe disability and dying. The decision-making needs to be continuously challenged as new injury patterns emerge relegating some older trauma dictums to a secondary role. Perhaps some things handled with a scalpel by the more "seasoned" surgeon are now better managed by the interventional radiologist! Conversely, the pendulum swing may also revert to being more adept at an open repair when austere locations and hemodynamics (or a lack thereof) do not allow for the calling in of a crew to open the hybrid suite! The pendulum will not rest. What is required of trauma surgeons is to always consider new ideas, unprejudiced by past successes or failures, accepting that there just might still be a better way when being entrusted with taking the last shot. Trauma surgery is mostly muscle memory and preparation. When precious minutes remain, many things must be considered, but a definitive decision must be made when competing against death.

The decision-making required to win at saving lives is the impetus for surveying authors from around the globe to write this book. Each author was given a specific clinical scenario to discuss, highlighting available data while offering their own expertise toward answering difficult branch points in the evaluation and

resuscitation of the injured patient, whether by operative intervention or with the utilization of trauma adjuncts. We hope that this text will serve as an informative guide aligning evidence-based medicine with the need for flexibility and improvisation when treating the injured patient. Prevailing practices by prominent programs, iconic individuals, and a lack of uniformity in patient presentations with underpowered studies alongside a myriad of other factors make analyses difficult. When the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was created in the year 2000, the intent was to formulate to what extent one could be confident about the quality and strength of recommendations. We assembled experts on each topic in this book to think hard about discrepancies and asked for them to assign a GRADE to each chapter based upon literature review. In addition, each chapter concludes with *"A personal view of the data"* allowing the authors' personal opinion of the data and the application of the data. The inclusion of this short description makes absolute sense because the unscripted nature of trauma often requires deviation from dogma.

All practice locations are not level I academic trauma centers replete with residents, surgical subspecialists, interventional radiologists, and rapidly replenishing blood banks. Globally more lives are saved with far less away from academic centers. This book was created specifically as a resource for community surgeons that have a stake in saving lives and decreasing the sequelae of injury with far less than many of the institutions represented in this text. Despite the authors' affiliations with exceptional academic centers and many years of personal experience, they were requested to present their evaluations of the literature based upon the GRADE criteria as detailed below:

High	There is a lot of confidence that the true effect lies close to that of the estimated effect.
Moderate	There is moderate confidence in the estimated effect: The true effect is likely to be close to the estimated effect, but there is a possibility that it is substantially different.
Low	There is limited effect in the estimated effect: The true effect might be substantially different from the estimated effect.
Very low	There is very little confidence in the estimated effect: The true effect is likely to be substantially different from the estimated effect.

Each chapter was superbly written by the contributing authors and offers practical guidance in addressing difficult decisions in trauma surgery.

Chicago, IL, USA — Kenneth Wilson
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Acknowledgement

Producing this book was a challenge amid a worldwide pandemic. We want to express our sincerest gratitude to all the authors and co-authors that had every reason to decline our requests and focus solely on being clinicians, community leaders or delving deeper into administrative roles during the challenge of the COVID-19 pandemic. Trauma surgery itself lends to compassion fatigue, burn-out, and stress disorders; however, lockdowns, social distancing, and self-isolation from family, and community health concerns during this crisis only exacerbated the challenges of being a trauma surgeon. Thank you for your perseverance and resilience.

Many thanks to Prakash Jagannathan and the entire Springer team that allowed for deadline extensions during this challenging time in our history.

I am indebted to my wife Nichole and four children, Dakota, Cheyenne, Rebekah, and Gabrielle that allowed me to spend many hours away from home to complete this project. I also want to thank Dr. Rogers and Dr. Ferguson, both of whom entrusted me with their vision of creating the inaugural text of Difficult Decisions in Trauma Surgery.

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Contents

Part I

Resuscitation

Difficult Decisions in Trauma: Is ABC the Right Mantra?

1

John M. Ruggero and Matthew J. Martin

Introduction

Current practice in most modern civilian trauma centers follows the Advanced Trauma Life Support (ATLS) prioritized approach to evaluation and intervention focusing on Airway (A) Breathing (B) and Circulation (C) ("the ABCs") in the initial assessment of trauma patients. This has been the mainstay of traumatic resuscitation since ATLS's inception and widespread acceptance throughout the medical community. The evidence supporting the pathway and ordering of priorities in the ABC approach is based on expert consensus with little literature to support its clinical application [1]. In approaching this question, it is critically important to understand the principles and rationale behind the "ABC" mantra, the existing epidemiologic and outcome data that supports or refutes this approach, and the likely impact of any program to alter this ingrained sequence in the initial trauma evaluation and resuscitation process.

The rationale and purpose for the ATLS primary survey is to rapidly identify any immediately life-threatening pathology or injuries, to prioritize these from most important to least important, to begin interventions to address the identified problem,

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and to essentially ignore all other non-emergent injuries or problems until later in the evaluation. Although it seemingly makes sense that without a patent airway a patient will rapidly progress to cardiorespiratory arrest, there is little available data that airway should be prioritized in sequence over circulatory and hemorrhage concerns. From an epidemiologic standpoint the incidence of complete airway loss after trauma is relatively low, particularly among survivors to EMS arrival and/or hospital arrival. In comparison, circulation and bleeding issues are much more prevalent and likely causes of early mortality or morbidity, and thus from a simple likelihood standpoint should arguably be prioritized over airway.

If strictly adhering to the dogma of "A" interventions first, especially in a hemodynamically unstable trauma patient, there is a potential to perpetuate or worsen the physiologic derangements that frequently occur with intubation, specifically rapid sequence intubation (RSI). The vasodilatory effects caused by RSI in addition to the effects of positive pressure ventilation may further compromise a hypovolemic/bleeding patient by putting them at risk for more significant hypotension and decreased cardiac output leading to an overall decrease in perfusion [2–6]. For patients in class 3–4 hemorrhagic shock who are awake and have a patent airway, administration of agents that usually include some combination of paralytic and sedative/analgesia often produce a precipitous drop in perfusing pressure, loss of muscle tone, and blunting of the normal catecholamine response. The end result of this is frequently severe instability or rapid progression to cardiac arrest and the need for cardiopulmonary resuscitation while attempting to "catch up" on the resuscitation.

Based on the experiences during military conflicts of the last two decades we have seen the benefits of an aggressive focus on prioritization of "C" interventions focused on hemorrhage control over the usual "A" interventions. This includes prehospital placement of tourniquets, hemostatic dressings, and the use of blood products for resuscitation of hypotensive severely injured trauma patients. These novel techniques have been adopted by many civilian trauma centers and applied to their population [7]. This benefit has been adapted by the military's Tactical Combat Casualty Care (TCCC) course, which uses the approach of controlling life-threatening hemorrhage first prior to airway interventions. This changes the ABC mnemonic of ATLS to either CCAB (Catastrophic hemorrhage; Circulation; Airway; Breathing) or MARCH (Massive hemorrhage; Airway; Respiration; Circulation; Head/Hypothermia). This doctrine is widely accepted as best practice in the realm of military medicine and has yielded numerous improvements in battlefield medicine [8–10]. This approach has also gained significant acceptance among the civilian trauma community in both the pre-hospital and in-hospital phases of care. Numerous efforts aimed at early hemorrhage control and hemostatic resuscitation have been adopted, such as the American College of Surgeons "Stop the Bleed" course, the increased utilization of pre-hospital blood products, and the currently increasing adoption of whole blood for initial trauma resuscitation at many centers.

Simultaneously, there have been no corresponding initiatives with a focus on increasing the utilization of early airway interventions, and in fact many trauma systems have attempted to decrease or even eliminate the use of pre-hospital intubation in select trauma populations.

In addition to the above-mentioned military and civilian trauma community's focus on circulation first there also has been a significant shift in the medical literature in regard to cardiopulmonary resuscitation of medical patients. Focus has been shifted from acquiring an airway or delivering "rescue breaths" first to prioritizing circulation by initiating continuous chest compressions without pauses for airway interventions. These approaches are now widely taught in the Basic Life Support (BLS) and Advanced Cardiac Life Support (ACLS) courses and highlight how the most high-yield interventions to improve outcomes should focus on restoring adequate circulation and central perfusion rather than waste critical minutes on less effective airway interventions or assessments. This has led to overall better outcomes in this population in a number of large analyses and from a variety of causes of cardiopulmonary arrest [11–14].

Obviously, changing the practice and utilization of a uniform and very well-entrenched algorithm such as the "ABCs" approach to severely injured trauma patients is a major challenge. It is currently being adopted in multiple centers across the globe; however, the long-term clinical advantages should be based on sound scientific evidence instead of expert consensus. In this chapter we discuss the literature on the paradigm shift of adopting an approach based on hemorrhage control first prior to airway interventions.

Search Strategy

Our search strategy was to use PUBMED using the keywords airway, circulation, intubation, hemorrhage control, hypotension, pre-hospital, and ATLS. We focused on the two primary PICO questions as shown in Table 1.1. We included and reviewed manuscripts from 1990 to 2020.

Table 1.1 PICO questions for the issue of airway first versus circulation first approach

P (patients)	I (intervention)	C (comparator)	O (outcomes)
Trauma patients in extremis/ hypotensive (in hospital)	Addressing circulation first CAB	Addressing airway first ABC	Mortality Hypotension Transfusion requirements
Trauma patients in extremis/ hypotensive (pre-hospital)	Addressing circulation first CAB	Addressing airway first ABC	Mortality Hypotension Transfusion requirements

Results

Military Experience

As previously mentioned, the military has systematically adopted a practice of assessing for and controlling life-threatening hemorrhage first prior to addressing airway issues. This change in practice was due to the prominence of hemorrhage as a cause of death in that specific patient population. Hemorrhage is the leading cause of potentially preventable death on the battlefield, with the torso identified as the primary focus [15–18]. A study by Kelly et al. examined the cause of deaths from Operation Iraqi Freedom and Operation Enduring Freedom from 2003–2004 and compared them to those of 2006. The main cause of death in potentially survivable patients was hemorrhage that contributed to 85% of the deaths [17]. Holcomb et al. reported similar significance of hemorrhage as a cause of death (82%) in the analysis of deaths in Special Operations forces over a similar time period [15]. Both of these studies also demonstrated that the majority of deaths (and opportunities for improvement) occurred in the pre-hospital environment. Subsequently, Martin et al. analyzed a series including only in-hospital deaths at a combat support hospital and found the prominence of hemorrhage related deaths to be 32%, which was second only to severe head injury at 45% [19]. In all of these studies, airway issues were not reported as a significant cause of death and particularly among preventable or potentially preventable deaths. The data is clear that in severely injured military trauma patients the key maneuver in preventing preventable mortality is to address hemorrhage control and circulation first, and that training/equipment programs should focus on this area versus airway interventions. This has led to multiple institutions adopting new protocols such as addressing circulation prior to airway and the concept of taking a patient directly to the operating room and bypassing the trauma bay. Each of these concepts will be discussed further in the next sections.

Circulation First

The adoption of "C" interventions prior to "A" interventions has already been cemented into the civilian non-trauma medical community and BLS/ACLS courses. Recent publications in the medical literature support the shift in focus of protocols moving from acquiring an airway first, to prioritizing perfusion by initiating chest compressions expeditiously especially in patients with a primary cardiac event. This has resulted in better outcomes in the reported medical literature [11–14]. Although there are large bodies of literature in the trauma setting regarding airway management with early intubation ("A") and hemorrhage control/resuscitation ("C"), there are very few studies that have compared and contrasted these two directly or evaluated differences related to their priority and sequencing by the trauma team.

One recent American Association for the Surgery of Trauma (AAST) multicenter trial conducted by Ferrada et al. did directly investigate this critical question [20]. The authors conducted a retrospective analysis of all patients that presented to

trauma centers with presumptive hypovolemic shock and undergoing intubation in the trauma bay. There were 440 patients included from 12 level 1 trauma centers. 245 (55.7%) received intravenous blood product resuscitation first, and 195 (44.3%) were intubated before any resuscitation was started. Analysis showed no statistical difference in overall mortality or other outcome measures between the two groups [20]. This study actually highlights the fact that despite the perpetuated sequence of ABC in most trauma management algorithms there are a significant proportions of trauma centers already performing "C" interventions first (over 50% in this sample). It also helps to dispel the fear that delaying airway evaluation and interventions/intubation in favor of resuscitation and hemorrhage control would result in higher mortality and worse neurologic outcomes. However, the retrospective nature and clear baseline differences between the two comparison groups limit any definitive conclusions about whether an approach focusing on "C" first is associated with improved outcomes.

A related and equally important study examined whether an aggressive posture of early intubation in the Emergency Department (ED) versus delaying intubation until arrival in the operating room (OR) was associated with any outcome differences among trauma patients requiring emergent surgery [21]. Among the 241 patients studied, 57% were intubated in the ED and 43% in the OR. Although there were no identified differences in patient demographics, injury types, initial hemodynamics, or injury severity, the incidence of post-intubation cardiopulmonary arrest was significantly higher (8% vs 0.9%) in the ED intubation cohort. Earlier ED intubation was also not associated with any benefit in terms of time to definitive surgery or hemorrhage control. This study helps to quantify the common experience of many trauma surgeons with post-intubation collapse and arrest in patients with hemorrhagic shock who undergo RSI prior to adequate resuscitation and/or hemorrhage control.

Pre-hospital/ER/OR Intubation

There is no doubt that the airway needs to be evaluated and addressed especially in an unstable trauma patient. However, the question still remains, where and when should this occur? There is significant evidence that in the bleeding or unstable trauma patient intervention in the pre-hospital setting without proper resuscitation will yield a worse overall outcome and delay the time to needed interventions or surgery. Sokol et al. reviewed the Department of Defense Trauma Registry looking at pre-hospital interventions in pediatric trauma patients, with interventions categorized into airway ("A") or circulation ("C") groups. Their analysis found that "A" interventions were associated with higher unadjusted mortality and remained independently associated with increased mortality after multivariate adjustment was performed [22]. In stark contrast, the "C" interventions were associated with a significant survival benefit among patients with major bleeding injuries. Non-military studies have yielded similar results of an increase in morbidity and mortality with pre-hospital airway interventions and intubation

[23, 24]. Some recent studies have gone even farther and investigated whether patients should have intubation delayed until the operating room [21]. In this analysis the authors were able to associate emergency department intubated patients with a higher chance of sustaining post-intubation traumatic cardiopulmonary arrest. This data suggests that control of hemorrhage and early initiation of resuscitation is critical to minimizing preventable complications related to airway interventions. Although a common theme in most trauma textbooks and ATLS for patients with major hemorrhage is to "minimize time in the ER" and transport them expeditiously to the OR, there is always some delay introduced by the ER evaluation. Several civilian trauma systems have introduced systems for "Direct to OR" trauma resuscitation where select patients are triaged directly to a fully equipped operating room for the initial evaluation and resuscitation [25–27]. This concept revolves around expeditiously getting the patient to the proper resources where control of hemorrhage and initiation of blood product resuscitation can be accomplished prior to or during the initiation of "A" interventions. The published series have demonstrated that this approach is associated with significantly shorter times to initiation of lifesaving interventions, faster hemorrhage control, and decreased mortality rates compared to predicted survival.

Recommendations Based on Data

In the pre-hospital setting, trauma patients with signs of ongoing hemorrhage or hemorrhagic shock should have "C" assessments and interventions performed before "A" interventions. "C" assessments and interventions should include tourniquets, direct pressure, and balanced resuscitations with component therapy or whole blood.

Rapid sequence intubation (RSI) in the presence of ongoing hemorrhage, cardiac tamponade, and hemorrhagic shock can produce precipitous instability and cardiovascular arrest. RSI should be delayed whenever possible until hemodynamic stabilization, and until adequate initial resuscitation is begun in a setting equipped for immediate hemorrhage control.

In most settings the reality is that the "A" and "C" assessments and temporizing interventions should be done simultaneously. However, major trauma victims are more likely to die from hemorrhage/circulation issues than airway issues, and hemorrhage and circulation concerns should take priority.

Summary of Recommendations

- In the military trauma population, the key maneuver in avoiding preventable mortality is to address hemorrhage control and circulation first. Civilian and military training programs should focus on this area versus airway interventions (Evidence quality high; strong recommendation).

- Delaying airway evaluation and interventions/intubation in favor of resuscitation and hemorrhage does not result in higher mortality and worse neurologic outcomes (Evidence quality poor; moderate recommendation).
- In the pre-hospital setting, "A" interventions are associated with higher unadjusted mortality and increased mortality after multivariate adjustments, while "C" interventions are associated with a significant survival benefit among patients with major bleeding injuries (Evidence quality moderate; moderate recommendation).
- In all cases with signs of shock, RSI should not be performed until some form of resuscitation is begun and preferably the bleeding has been controlled or will be controlled shortly (Evidence quality moderate; moderate recommendation).

Personal View of the Data

The motto of the military Joint Trauma System is "Right patient, right place, right time, right care," and really distills the essence of the recent large volume of experience with severely injured and bleeding combat casualties. With real-time analyses of data from both military and civilian trauma deaths, it became apparent that hemorrhage and hemorrhage control should clearly replace "airway" as the primary concern and focus in the pre-hospital and early in-hospital phases of care. Although lack of an airway can certainly produce rapid death, the probabilities and likelihood of survival weigh much more heavily in favor of hemorrhage control measures versus airway interventions or intubation. In reality at modern trauma centers, these assessments and interventions should be performed simultaneously and not in the strict "ABCD" sequence taught by ATLS, but the ordering is important for shaping how providers and particularly trainees think about and prioritize these problems. We also must distinguish what is particularly harmful about focusing on "A" first versus what is relatively harmless in the big picture.

This combination of bedside exam and imaging can be done in a matter of minutes and should reliably identify or rule out sites of major hemorrhage. For external hemorrhage the immediate focus should be on direct wound management, tourniquet/hemostatic dressing placement, and any other adjunct to stop the visible bleeding. For non-compressible truncal hemorrhage, the focus should be on rapid transport to a setting where operative hemorrhage control can be obtained, with simultaneous initiation of controlled resuscitation with blood products when available. In both cases, basic airway maneuvers should then be performed based on the airway assessment, but rapid sequence intubation should be avoided if possible. Only in the rare situation of a mechanical airway obstruction or significantly prolonged transport times should emergent RSI or a surgical airway be required. In all cases with signs of shock, RSI should not be performed until some form of resuscitation is begun and preferably the bleeding has been controlled or will be controlled shortly. For patients being evaluated in the ER and who clearly need operative hemorrhage control, we should avoid what I call the "ER full meal deal" where the team delays transport to perform intubation, place a central venous line and/or arterial

line, and give multiple rounds of blood products. All of these things can be delayed until the patient is in the operating room and can then be performed as the surgeon is obtaining definitive hemorrhage control. So in these authors' opinion, and in response to this chapter title, "ABC" should NOT be the standard mantra for bleeding trauma patients. The military approach with "C" assessment and interventions first should be the new standard of care and will hopefully avoid the predictable and preventable mortality and morbidity associated with premature RSI and intubation in the unstable patient.

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2 Difficult Decisions in Trauma Surgery: What Is the Clinical Impact of Whole Blood as Compared to Component Therapy in Civilian Trauma?

Lane L. Frasier, Andrew J. Benjamin, C. William Schwab, and Jeremy W. Cannon

Introduction

Whole blood transfusion was the standard of care for patients with traumatic injuries during World War I and II and the Korean War, with >600, 000 units of whole blood transfused during the Korean War [1]. In the 1960s, blood banks began separating donated blood into component therapy, prolonging storage times and allowing transfusions for specific requirements (e.g., transfusing only platelets for patients with thrombocytopenia). With this shift in blood bank practices, surgeons also changed their transfusion practices for management of patients with traumatic injuries, incorporating large volume crystalloid, followed by packed red blood cells (pRBCs) with low ratios of fresh frozen plasma (FFP) and platelets. This was accompanied by risks of coagulopathy, fluid overload, and abdominal compartment syndrome. Although damage control resuscitation practices (DCR) mitigate some of these adverse effects, even balanced component resuscitation with 1:1:1 component therapy of pRBCs to FFP to platelets yields a relatively anemic, thrombocytopenic, and hypo-coagulable product for infusion [2].

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Recently, there has been renewed interest in resuscitating patients with traumatic hemorrhage with whole blood. Proponents argue that this approach replaces all the components that lost with traumatic hemorrhage with a much lower volume of additives that contribute to ongoing coagulopathy.

During the recent conflicts in Iraq and Afghanistan, the U.S. military permitted the transfusion of whole blood when component blood products were not available in sufficient quantities to enable adequate resuscitation of patients with traumatic injuries. In the austere environment, sufficient quantities of pRBCs and FFP can be difficult to maintain, and apheresis platelets are very rarely available due to the ultra-short shelf life of this product. Accordingly, many patients received whole blood transfusion as a substitute source of platelets. Observational studies reporting non-inferiority and possibly a clinical benefit further renewed interest in use of whole blood for treating traumatic hemorrhage.

This chapter summarizes the current literature regarding whole blood transfusion for treatment of traumatic hemorrhage as compared to component therapy.

PICO Questions and Search Strategy

For this review, we developed three questions addressing a specific patient population (P), intervention (I), comparators (C), and outcomes of interest (O) (Table 2.1). A systematic review of the literature addressing these three PICO questions was performed using MEDLINE and EMBASE databases to identify English-language studies published before January 2020 using the medical subject heading (MeSH) terms and keywords. All studies including randomized controlled trials (RCTs), observational studies, and retrospective studies were evaluated. Quantitative analysis was performed using Review Manager (RevMan) 5.2 (Copenhagen, Denmark).

Relevant outcomes were identified by the chapter authors and rank ordered in terms of importance for medical decision-making and perceived patient preference. These included mortality, specific complications including multi-system organ failure (MSOF), venous thromboembolism (VTE) including deep venous thrombosis (DVT) and pulmonary embolism (PE), and transfusion reactions. Outcomes were scored from 1 (critical for decision-making) to 10 (not important for decision-making) using Research Electronic Data Capture (REDCap) hosted by the University of Pennsylvania (Table 2.2).

Table 2.1 PICO questions

Patients (P)	Interventions (I)	Comparators (C)	Outcomes (O)
Acutely bleeding patients	Transfusion with whole blood	Component therapy	Improved mortality at 24-h and 30 days
Acutely bleeding patients	Transfusion with whole blood high titer	Transfusion with whole blood low titer	Multi-system organ failure (MSOF)
Acutely bleeding woman of childbearing age	Transfusion with whole blood	Component therapy	Risk of antibody formation

Table 2.2 Rank order of outcomes of interest

Outcome	Sub-category	Score[a]
Mortality	Death from hemorrhage >24-h mortality >30-day/hospital mortality >6-h mortality	2
Any complication	MSOF > respiratory > renal > infectious > VTE	4
Total blood product requirement		4
Any transfusion reaction		5
Hemolysis		6
Volume of anticoagulant		6
Expense		6
Transfusion logistics		8

MSOF multi-system organ failure, *VTE* venous thromboembolism
[a]1–3 = Critical for decision-making; 4–7 = Important but not critical for decision-making; 8–10 = Less important for decision-making, of lower importance to patients

Results

Results for Mortality (PICO 1)

In the acutely bleeding trauma patient, does transfusion with whole blood compared to component therapy result in improved mortality at 24-h and 30-days?

Qualitative Synthesis

A meta-analysis by Crowe et al. [3] identified 12 studies (total of 8431 patients) evaluating mortality outcomes at 24 h, 30 days, or in-hospital. They identified significant heterogeneity of populations, settings, interventions, and studied outcomes, and found no differences in mortality when patients received whole blood versus component therapy.

Cotton et al. [4] report on a randomized controlled pilot trial of modified whole blood (leukoreduced, resulting in platelet depletion) compared to component therapy for civilian trauma patients with severe trauma and predicted to require massive transfusion.

Seheult et al. [5] described a retrospective analysis of 135 civilian trauma patients who received low-titer whole blood transfusion (LTWB, defined here as) who were propensity-matched 1:1 to civilian trauma patients who received ≥1 unit pRBC during their first 24 h after admission. The authors found no significant differences in 24-h or in-hospital mortality between patients receiving component therapy without LTWB compared to patients who received LTWB (6-h mortality 3.7% vs 3.0%, $p = 0.74$; 24-h mortality 12.6% vs 8.9%, $p = 0.33$; in-hospital mortality 18.5% vs 24.4%, $p = 0.24$).

Jones and Frazier [6] describe a retrospective analysis of the 2009 National Trauma Data Bank to perform logistic regression and identify predictors of mortality. Analyzing 1745 patients ages 18–45 with major trauma, defined as Injury Severity Score (ISS) > 25, the authors found that higher ISS, longer pre-hospital transfer time, and transfusion with component blood products were independently associated with mortality. Component therapy was associated with a higher odds ratio (3.164, 95% CI 1.314–7.618, $p = 0.01$) of overall mortality compared to whole blood transfusion. Neither 6-h nor 24-h mortality was reported in this analysis.

Nessen et al. [7] performed a retrospective analysis of 488 military trauma patients who received fresh whole blood (FWB) in addition to pRBC and fresh frozen plasma (FFP) in Afghanistan, where platelet component therapy was not readily available, compared to patients who did not receive FWB. They found that patients who received FWB in addition to pRBC and FFP component therapy had lower in-hospital mortality (OR 0.096, 95% CI 0.02–0.55, $p = 0.008$) despite having higher ISS. A subset analysis of patients who received uncrossmatched Type O FWB (N = 46) compared to type-specific FWB (N = 48) found no difference in mortality. Neither 6-h nor 24-h mortality was reported in this analysis.

A similar retrospective analysis by Auten et al. [8] yielded conflicting results. This smaller analysis of 61 US military trauma patients with ISS ≥ 15 was performed, evaluating outcomes for patients who received component therapy with pRBC and FFP (N = 35) vs component therapy plus FWB (N = 26) found no survival benefit at 24 h or 30 days for patients receiving component therapy plus FWB using logistic regression (OR 0.81, 95% CI 0.08–7.82).

Perkins et al. [9] performed a retrospective analysis of military trauma patients in Iraq requiring massive transfusion, defined as ≥10 units of blood products in 24 h and compared patients receiving component platelets (N = 284) vs those receiving FWB (N = 85). Using multivariate regression, the authors found no difference in survival between patients receiving component platelets vs FWB as part of their massive transfusion resuscitation at 24 h ($p = 0.06$). Mortality was not reported at 6 h in this analysis.

Spinella et al. [10] report a retrospective analysis of military personnel with traumatic injuries between 2004 and 2007, who received whole blood, but not component platelets, in addition to component therapy with pRBC and FFP (N = 100), compared to patients who underwent component therapy with pRBC, FFP, and platelets (N = 254). Reported outcomes included 24-h and 30-d mortality. Using multivariate regression, use of whole blood, and increasing volumes of whole blood transfusion, were associated with improved 30-day survival.

Yazer et al. [11] reported outcomes for male patients with traumatic injuries and hemorrhage requiring blood transfusion, comparing outcomes for 47 patients who received 1–2 units of whole blood to 145 historical controls who required transfusion within 24 h of admission. They reported no difference in mortality for patients receiving 1–2 units of whole blood (36%) compared to historical controls (28%), $p = 0.27$.

Kauvar et al. [12] evaluated 281 military trauma patients who received blood transfusion in 2003. Thirty-six of these patients received FWB transfusion. Although

mortality data were missing for 6% of patients not receiving FWB, overall mortality did not differ between groups. Mortality was not reported at 6 or 24 h in this analysis.

Zhu et al. [13] review outcomes for severely injured trauma patients requiring blood products pre-hospital. They report on 25 adult (22 traumatically injured) patients who received whole blood en route to hospital. They report gross mortality rate (36%) including pre-hospital deaths, and compare to historical controls (62%). Ho and Leonard [14] review 353 patients who received massive transfusion protocol, 77 of whom received whole blood during their massive transfusion. Only 25% of patients in the massive transfusion group overall carried a diagnosis of trauma, however (12% of the whole blood recipients and 30% of standard MTP).

Quantitative Synthesis

Five articles met criteria for quantitative analysis of 24-h mortality (Fig. 2.1), and 11 articles met criteria for quantitative analysis of 30-day or in-hospital (Fig. 2.2) mortality. Both are sub-divided by intervention with stored whole blood, common in civilian and military settings, and fresh whole blood, used nearly exclusively in the military setting. Interventions with stored whole blood demonstrate low heterogeneity, while interventions with fresh whole blood had a moderate degree of heterogeneity. The combined effect showed no benefit with a low degree of heterogeneity.

Grading the Evidence

The overall quality of the evidence was Low (30-day mortality) to Very Low (6-h and 24-h mortality) due to the retrospective nature of most data, high risk of bias, and imprecision of reported outcomes. Funnel plots evaluating risk of publication bias are seen in Fig. 2.3. There is the potential for publication bias for 24-h mortality, indicated by the lack of publications occupying the lower

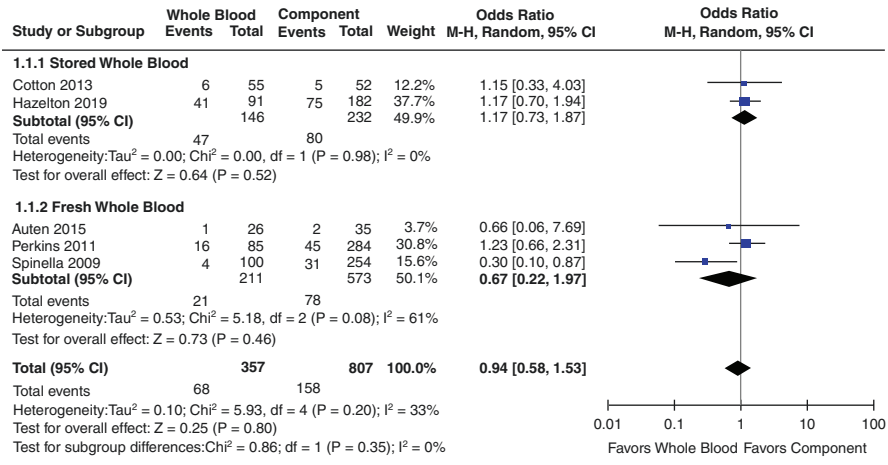

Fig. 2.1 Quantitative analysis of 24-h mortality (PICO 1). Articles are sub-grouped by intervention using stored whole blood or fresh whole blood. *CI* Confidence Interval

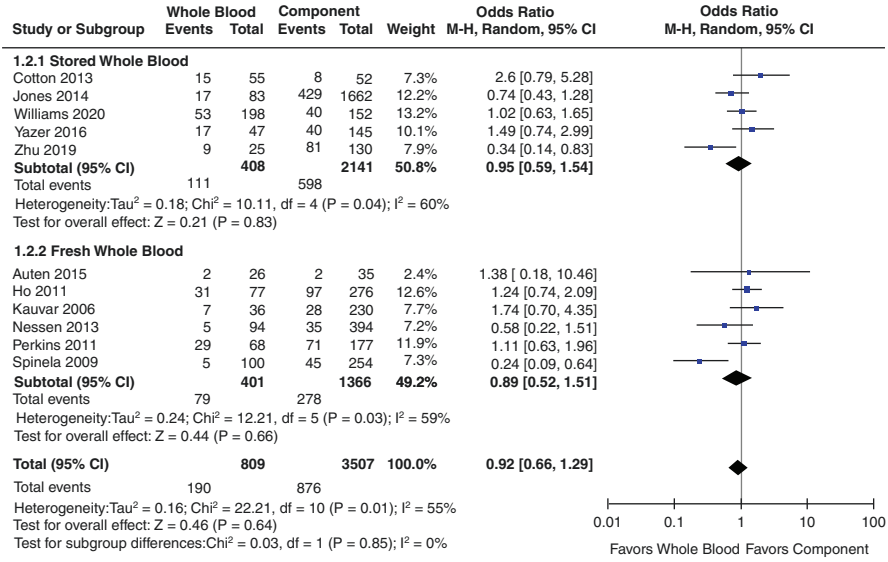

Fig. 2.2 Quantitative analysis of 30-day mortality (PICO 1). Articles are sub-grouped by intervention using stored whole blood or fresh whole blood. *CI* Confidence Interval

right corner of the plot. There was a low likelihood of publication bias for 30-day mortality.

Results for Any Complications (PICO 2)

For the acutely bleeding trauma patient, does transfusion with whole blood with high vs low antibody titer result in increased multi-system organ failure (MSOF) at 30 days?

Qualitative Synthesis

We identified no articles that addressed this question. There is currently no standard definition of "high" or "low" titer whole blood, and individual institutions and blood banks must determine their own standards for the definition of "low" titer [15] given the availability of donors and the risks of wasting donated blood versus the risks of antibody-mediated transfusion reaction. Additionally, there were few articles that evaluated MSOF after whole blood transfusion. We therefore amended our search to identify any complications associated with whole blood transfusion.

Seheult et al. [5] evaluated Acute Kidney Injury (defined as any of the following: increased creatinine 1.5x over baseline, absolute increase in creatinine ≥0.5 mg/dL, or any post-admission creatinine ≥4.0 mg/dL) and bacteremia, defined as any positive bacterial blood culture within 7 days of admission. Auten et al. [8] evaluated complications including coagulopathy, any infection, blood

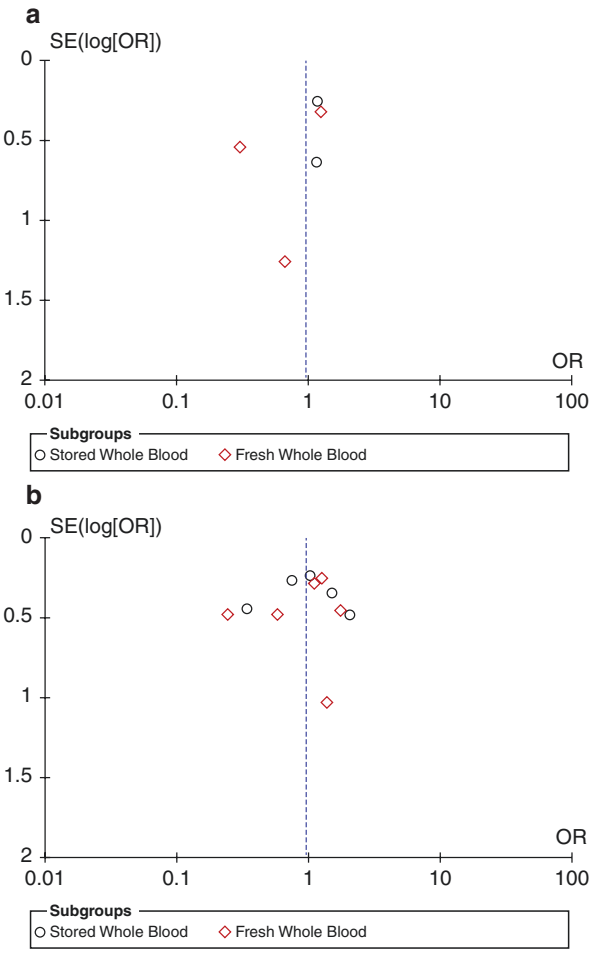

Fig. 2.3 Funnel plots analyzing risk of publication bias for 24-h (**a**) and 30-day (**b**) mortality (PICO 1). Articles are sub-grouped by intervention using stored whole blood or fresh whole blood

clotting, transfusion reaction, and Acute Respiratory Distress Syndrome (ARDS). Perkins et al. [9] evaluated complications including ARDS, MOFS, infection, embolic event. Spinella et al. [10] evaluated complications including DVT, PE, myocardial infarction (MI), cerebral stroke, ARDS, and renal failure, which were not defined in the manuscript.

Quantitative Synthesis

Cotton [4], Perkins [9], and Spinella [10] included data appropriate for meta-analysis of complications data (Table 2.3). Overall, there was a trend toward increased complications with use of whole blood transfusion (Fig. 2.4). This increase in reported complication with use of whole blood may represent survivorship bias, driven by the increased survival reported with whole blood transfusion by Spinella [10].