Timing of major fracture care in polytrauma patients – An update on principles, parameters and strategies for 2020 — Source link

H-C Pape, Sascha Halvachizadeh, L.P.H. Leenen, G D Velmahos ...+2 more authors

Institutions: University of Zurich, University Medical Center Utrecht, Harvard University, University of Calgary ...+1 more institutions

Published on: 01 Oct 2019 - Injury-international Journal of The Care of The Injured (Elsevier)

Topics: Trauma center, Resuscitation and Polytrauma

Year: 2019

Timing of major fracture care in polytrauma patients – an update on principles, parameters and strategies for 2020

Pape, H-C ; Halvachizadeh, Sascha ; Leenen, L ; Velmahos, G D ; Buckley, R ; Giannoudis, P V

Abstract: Objectives Sustained changes in resuscitation and transfusion management have been observed since the turn of the millennium, along with an ongoing discussion of surgical management strategies. The aims of this study are threefold: a) to evaluate the objective changes in resuscitation and mass transfusion protocols undertaken in major level I trauma centers; b) to summarize the improvements in diagnostic options for early risk profiling in multiply injured patients and c) to assess the improvements in surgical treatment for acute major fractures in the multiply injured patient. Methods I. A systematic review of the literature (comprehensive search of the MEDLINE, Embase, PubMed, and Cochrane Central Register of Controlled Trials databases) and a concomitant data base (from a single Level I center) analysis were performed. Two authors independently extracted data using a pre-designed form. A pooled analysis was performed to determine the changes in the management of polytraumatized patients after the change of the millennium. II. A data base from a level I trauma center was utilized to test any effects of treatment changes on outcome. Inclusion criteria: adult patients, ISS $>$ 16, admission $<$ less than 24 h post trauma. Exclusion: Oncological diseases, genetic disorders that affect the musculoskeletal system. Parameters evaluated were mortality, ICU stay, ICU complications (Sepsis, Pneumonia, Multiple organ failure). Results I. From the electronic databases, 5141 articles were deemed to be relevant. 169 articles met the inclusion criteria and a manual review of reference lists of key articles identified an additional 22 articles. II. Out of 3668 patients, 2694 (73.4%) were male, the mean ISS was 28.2 (SD 15.1), mean NISS was 37.2 points (SD 17.4 points) and the average length of stay was 17.0 days (SD 18.7 days) with a mean length of ICU stay of 8.2 days (SD 10.5 days), and a mean ventilation time of 5.1 days (SD 8.1 days). Both surgical management and nonsurgical strategies have changed over time. Damage control resuscitation, dynamic analyses of coagulopathy and lactate clearance proved to sharpen the view of the worsening trauma patient and facilitated the prevention of further complications. The subsequent surgical care has become safer and more balanced, avoiding overzealous initial surgeries, while performing early fixation, when patients are physiologically stable or rapidly improving. Severe chest trauma and soft tissue injuries require further evaluation. Conclusions Multiple changes in management (resuscitation, transfusion protocols and balanced surgical care) have taken place. Moreover, improvement in mortality rates and complications associated with several factors were also observed. These findings support the view that the management of polytrauma patients has been substantially improved over the past 3 decades.

DOI: https://doi.org/10.1016/j.injury.2019.09.021

Originally published at:
Pape, H-C; Halvachizadeh, Sascha; Leenen, L; Velmahos, G D; Buckley, R; Giannoudis, P V (2019). Timing of major fracture care in polytrauma patients – an update on principles, parameters and strategies for 2020. Injury, 50(10):1656-1670.
DOI: https://doi.org/10.1016/j.injury.2019.09.021

Journal Pre-proof

Timing of major fracture care in polytrauma patients – an update on principles, parameters and strategies for 2020

H.-C. Pape, S. Halvachizadeh

PII: S0020-1383(19)30538-8
DOI: https://doi.org/10.1016/j.injury.2019.09.021
Reference: JINJ 8323

To appear in:

L. Leenen

PII: S0020-1383(19)30538-8
DOI: https://doi.org/10.1016/j.injury.2019.09.021
Reference: JINJ 8323

To appear in:

G.D. Velmahos

PII: S0020-1383(19)30538-8
DOI: https://doi.org/10.1016/j.injury.2019.09.021
Reference: JINJ 8323

To appear in:

R. Buckley

PII: S0020-1383(19)30538-8
DOI: https://doi.org/10.1016/j.injury.2019.09.021
Reference: JINJ 8323

To appear in:

P.V. Giannoudis

PII: S0020-1383(19)30538-8
DOI: https://doi.org/10.1016/j.injury.2019.09.021
Reference: JINJ 8323

To appear in:

Please cite this article as: Pape H-C, Halvachizadeh S, Leenen L, Velmahos GD, Buckley R, Giannoudis PV, Timing of major fracture care in polytrauma patients – an update on principles, parameters and strategies for 2020, *Injury* (2019), doi: https://doi.org/10.1016/j.injury.2019.09.021

Title

Timing of major fracture care in polytrauma patients – an update on principles, parameters and strategies for 2020.

Pape, H.-C.[1], Halvachizadeh, S.[1], Leenen, L.[2], Velmahos, G.D.[3], Buckley, R.[4], Giannoudis, P.V.[5]

Affiliations

1 Department of Trauma, University Hospital Zurich, University of Zurich, Raemistrasse 100, 8091 Zurich, Switzerland, email: hans-christoph.pape@usz.ch

2 Department of Trauma | University Medical Centre Utrecht | Suite G04.228 |

Heidelberglaan 100 | 3585 GA Utrecht | The Netherlands, email: lleenen@umcutrecht.nl

3 Dept. of Trauma, Emergency Surgery and Critical Care, Harvard University, Mass. General Hospital, 55 Fruit St. Boston MA, 02114, USA

4 Section of Orthopedic Trauma, University of Calgary, Foothills Medical Center, 0490 McCaig Tower, 3134 University Drive NW Calgary, Alberta, T2N 5A1, CAN email: buckclin@ucalgary.ca>

5 Trauma & Orthopaedic Surgery, Clarendon Wing, A Floor, Great George Street, Leeds General Infirmary University Hospital, Leeds, LS1 3EX, UK, University of Leeds, UK, pgiannoudi@aol.com

Corresponding Author:

Hans-Christoph Pape

Rämistrasse 100

8091 Zurich

Hans-Christoph.Pape@usz.ch

Level of Evidence: III

Abstract

Objectives: Sustained changes in resuscitation and transfusion management have been observed since the turn of the millennium, along with an ongoing discussion of surgical management strategies. The aims of this study are threefold: a) to evaluate the objective changes in resuscitation and mass transfusion protocols undertaken in major level I trauma centers; b) to summarize the improvements in diagnostic options for early risk profiling in multiply injured patients and c) to assess the improvements in surgical treatment for acute major fractures in the multiply injured patient.

Methods:

I. A systematic review of the literature (comprehensive search of the MEDLINE, Embase, PubMed, and Cochrane Central Register of Controlled Trials databases) and a concomitant data base (from a single Level I center) analysis were performed. Two authors independently extracted data using a pre-designed form. A pooled analysis was performed to determine the changes in the management of polytraumatized patients after the change of the millennium.

II. A data base from a level I trauma center was utilized to test any effects of treatment changes on outcome. Inclusion criteria: adult patients, ISS > 16, admission < less than 24 hours post trauma. Exclusion: Oncological diseases, genetic disorders that affect the musculoskeletal system. Parameters evaluated were mortality, ICU stay, ICU complications (Sepsis, Pneumonia, Multiple organ failure).

Results:

I. From the electronic databases, 5,141 articles were deemed to be relevant. 169 articles met the inclusion criteria and a manual review of reference lists of key articles identified an additional 22 articles.

II. Out of 3,668 patients, 2,694 (73.4%) were male, the mean ISS was 28.2 (SD 15.1), mean NISS was 37.2 points (SD 17.4 points) and the average length of stay was 17.0 days (SD 18.7 days) with a mean length of ICU stay of 8.2 days (SD 10.5 days), and a mean ventilation time of 5.1 days (SD 8.1 days).

Both surgical management and nonsurgical strategies have changed over time. Damage control resuscitation, dynamic analyses of coagulopathy and lactate clearance proved to sharpen the view of the worsening trauma patient and facilitated the prevention of further complications. The subsequent surgical care has become safer and more balanced, avoiding overzealous initial surgeries, while performing early fixation, when patients are physiologically stable or rapidly improving. Severe chest trauma and soft tissue injuries require further evaluation.

Conclusions:

Multiple changes in management (resuscitation, transfusion protocols and balanced surgical care) have taken place. Moreover, improvement in mortality rates and complications associated with several factors were also observed. These findings support the view that the management of polytrauma patients has been substantially improved over the past 3 decades.

Level of Evidence: III

Key words: polytrauma, resuscitation, soft tissue injuries, acid base changes, lactate clearance, coagulopathy, damage control.

INTRODUCTION

Over the last two decades complication rates in patients with multiple injuries have decreased (1, 2). The causes may partially lie in the improvement of safety factors, both for motor vehicle passengers (3, 4) and for pedestrians involved in motor vehicle accidents (MVA) (5). Apart from these road safety issues, numerous changes have been made in clinical patient management. There is no doubt that more precise identification of the patient at risk for complications in the early stages after trauma is available (6-9). Also, there is a higher awareness of life-threatening complications (10-13), possibly related to the availability of numerous clinical parameters and biomarkers for the prediction of clinical complications (14 - 17).

The observed improvement in outcome in a critically injured patient with fractures is also striking. Improvements in early diagnostic tools (15-17), surgical techniques and staged management of fracture fixation has been seen to play a role (18-22). In general, surgical treatment strategies have become more individualized (23), especially in life-threatening injuries to the chest, abdomen and for major fractures (24-28). In a similar fashion, endpoints of transfusion, management of coagulopathy and end points of resuscitation appear to have been better defined (29). Other interdisciplinary trauma care groups suggest that the improvement in outcome is also related to better management of coagulopathy, in addition to those achieved by balanced surgical strategies (9).

Although many of the studies mentioned above suggest changes in various factors (including management of resuscitation, coagulopathy, supplementation of blood products, and safe surgery), there is currently no review that summarizes these. To address this gap in the literature, we performed a systematic review that synthesizes the available evidence to inform clinical practice and to guide future research. The aims of this study are as follows:

1. To describe the changes in resuscitation and mass transfusion protocols in multiple injured patients with severe hemorrhage
2. To summarize the developments of diagnostic tools for early profiling of the multiple injured patient
3. To assess the quality and options of different surgical treatment strategies for acute major fractures in multiple injured patients
4. To compare the development and the outcome of multiple injured patient in literature with the database of one Level 1 trauma center

METHODS

Part 1: Systematic review

Eligibility criteria

This systematic review was conducted based on a prior review protocol registered with the International Register of Systematic Reviews (PROSPERO registration). The protocol and review have been prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines (30).

We focused on the following eligibility criteria for multiple injured patients: 1) Studies investigating changes in the management in parameters of resuscitation and mass transfusion protocols (treatment of nonsurgical bleeding), 2) Studies providing reliable information assessing diagnostic tools, including scoring systems, to facilitate profiling of multiple injured patients, 3) Studies that provide reliable information assessing fracture management in the multiple injured patient.

Case reports, defined as studies reporting data on a sample size of less than 5 patients were excluded in this study. There was no further restriction of study designs. Results from meeting abstracts were included in a separate analysis and only included when found to be relevant or promising enough to warrant future publication in a peer reviewed journal. This was deemed important to minimize publication bias and test the stability of our review's conclusion. Original articles were included if published between Jan 1, 1999 and May 15. 2019. No language restrictions were applied. Data sources include MEDLINE, Embase, Web of Science, and Cochrane Register of Controlled Trial database (CENTRAL), regional databases and references of included studies. Trials that reported about multiple injured patients and their incidence of complications were included. Disagreements were resolved in discussion.

Screening and Assessment of Eligibility

Two independent reviewers (HCP and PG), both with methodological expertise and with content expertise independently reviewed the titles and abstracts of articles identified in the literature searches in order to determine if the articles should be considered for inclusion. The reviewers erred on the side of inclusivity and any disagreements resulted in the article proceeding to full-text review. Subsequently, both authors independently reviewed the full-text articles that were identified in the title and abstract screening for final inclusion. Any conflicts were discussed in order to achieve consensus. Articles that met the inclusion criteria were selected for data extraction. The other reviewers (LL, SH, RB, and GV), all with methodological expertise and with content expertise performed an assessment for feasibility and plausibility and the content regarding the conclusions made.

Methodological Quality

Authors independently graded the methodological quality of each included study. Observational studies were evaluated using the Methodological Index for Non-Randomized Studies (MINORS) (31). Randomized controlled trials (RCTs) were assessed with the Cochrane Collaboration's Risk of Bias Tool (32). This review includes the following MeSH terms: Abbreviated Injury Scale, accidental Falls/statistics & numerical data, accidents, Traffic/statistics & numerical data, angiography/methods, algorithms, arteriovenous Fistula/etiology, Adult, Biomarkers/blood, arterial injury, Brain Injuries, Traumatic/blood, Brain Injuries, coagulopathy, clinical Coding/methods, consensus, Extravasation of Diagnostic and Therapeutic Materials/etiology, Female, Hemoperitoneum / etiology Humans, Injury Severity Score, Glasgow Coma Scale Traumatic/mortality, Injury Severity Score, / epidemiology, incidence, multiple trauma/diagnosis, Lactic Acid/blood, Lactic Acid/pharmacokinetics, Multiple Trauma/epidemiology, observer variation, prospective studies, registries, trauma centers/statistics &

numerical data, United States/epidemiology, Europe /epidemiology, Injury Severity Score, major fractures, Male, Patient Admission, Patient Selection, Retrospective Studies, Salvage Therapy, Spleen/injuries, Tomography, X-Ray Computed, Trauma Centers, Treatment Outcome, Violence/statistics & numerical data, Wounds, Nonpenetrating/complications, Wounds, Nonpenetrating/diagnosis, Wounds, Nonpenetrating/epidemiology, Predictive Value of Tests, Wounds, Nonpenetrating/therapy.

The following particular subheadings were selected by the reviewers: emergency room management and resuscitation strategies; Diagnostics and management of coagulopathy; Diagnostics of acid-base changes; Scoring and management of orthopedic injuries; Soft tissue injuries (e.g. chest trauma and thoracic trauma, reperfusion).

Part 2: Database analysis

The database includes multiply injured patients treated at one Level 1 trauma center, as pointed out in detail in previous publications (142,144).

Briefly, the database analysis was utilized as follows:

Inclusion / Exclusion criteria

The study population had to fulfil the following inclusion criteria: adult patients, treated due to polytrauma (ISS > 16 points) at one Level 1 trauma center, and an admission time of less than 24 hours after injury. Patients with oncological diseases, chronic diseases, and genetic disorders that affect the musculoskeletal system were excluded.

Data management

During the development of the data base, all injuries are classified by the trauma physician who also routinely performs scoring of injury severity. Approval by the local institutional review board (IRB) according to IRC guidelines (No. St. V. 01-2008) was obtained. Data include twice daily entries of clinical and physiological parameters and organ function scores during the first three weeks of admission. It contains data for clinical chemistry, hemostasis, and parameters associated with artificial ventilation. Admission data were documented for the emergency room, all further laboratory data were acquired on daily basis, if needed, several times per day. All complications were documented during the clinical course, including ICU scores, pneumonia, sepsis and adult respiratory distress syndrome.

Definitions

In hospital mortality described was diagnosed when a patient succumbed during the first hospital stay.

The *intensive care stay* (ICU-stay) summarized the time (days) between admission and discharge from the intensive care unit (ICU). The intermediate care stay (IMC-stay) was defined as between admission and discharge from the IMC.

Pneumonia was diagnosed according to the diagnoses in the manuscripts. Most of them used the following criteria; body temperature - at least 38.5°C and one of the following criteria; infiltrate on chest x-ray in the absence of ARDS or positive culture in bronchoalveolar lavage fluid.

Multiple organ failure (MOF) was diagnosed according to a scoring system, when available in the references.

For the purpose of the current study, a comparison was made for outcome-based parameters and the general mortality rate, the rate of 72-hour mortalities, and complications which were separately investigated.

Complications during the hospital stay were defined as those occurring during the stay of intensive care, such as Pneumonia, Multiple organ failure and Sepsis.

Group distribution

It was thought to account for the changes in surgical management for major fractures, and nonsurgical changes, such as volume management and transfusion guidelines.

In the current level I center, limitations of the amount of initial surgery (damage control techniques(33)) were not routinely performed before 2002. Damage control techniques were routinely performed thereafter. Later, a change in transfusion guidelines was developed after 2007.

Three different time periods were separated as follows:

Group no DC

(< 2002; no limitations in duration of surgery at day I)

Group DC

(2003 – 2007; application of damage control techniques for major fractures in unstable patients)

Group DC Tr

(> 2007; application of new transfusion guidelines in addition to staged surgical management)

Therefore, the three groups are thought to represent either changes in the surgical management (group no DC versus DC) and surgical versus nonsurgical management changes (group DC versus DC Tr), (9, 34).

Statistics

Nominally scaled and categorical variables were compared with Pearson Chi-square test, continuous variables with students t-test. Continuous variables are displayed as a mean with standard deviation (SD), categorical variables as numbers (n) and percentages (%). Fitted generalized linear models were used for predictive estimate of scoring systems. Odds ratios (OR) for prognosis of the different endpoints were calculated, along with 95% confidence intervals (CI). Tests were corrected for multiple testing if necessary. Proportions were evaluated using the Yates-corrected statistics. The relative risks of complications were calculated individually and expressed in OR. The associations between conventional parameters and death were evaluated using univariate analysis. Continuous variables are summarized as mean and standard deviation. Statistical significance was assumed at an alpha = 0.05. All calculations were performed using R Core Team (2018) (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org/).

RESULTS

Part 1: Systematic review

The electronic database search identified 5141 articles that were deemed to be relevant to the topics listed above. Following review of titles, abstracts, and independent assessment of potential studies, we identified 169 articles that met the inclusion criteria. The manual review of reference lists of key articles identified an additional 22 articles, the manual search of annual meeting abstracts identified 5 eligible abstracts (published in the abstract books of the Orthopaedic Trauma Association (OTA), European Society for Trauma and Emergency Surgery (ESTES), and European Federation of National Associations of Orthopaedics and Traumatology (EFORT), and American Academy of Orthopaedic Surgeons (AAOS)).

All included studies were published or presented after 2000. The majority of studies were single-center initiatives that were conducted in Europe or North America.

Resuscitation strategies

Resuscitation strategies have changed towards permissive hypovolemia. This change had an impact on the general patient outcome (9, 35, 36). The most important new information was gathered by reducing the amount of volume administered, “damage control resuscitation“ (29, 37-39). Moreover, a multi-center study (Pragmatic Randomized Optimal Platelet and Plasma Ratios, PROPPR) trial developed the massive transfusion strategy targeting a balanced delivery of plasma-platelet-red blood cell (RBC) in a ratio of 1:1:1 (40). It appears to result in improved survival at 3 hrs. post admission and a reduction in mortality caused by exsanguination in the first 24 hours compared with a 1:1:2 ratio (41). Multiple other study principles were concluded from those results (42, 43), (**Table I**).

Diagnostic tools for early profiling of the multiple injured patient

Coagulopathy

Among the studies indicative of posttraumatic coagulopathy, fifteen were relevant for trauma patients. Among these, five represent guidelines, multicenter studies or systematic reviews. They include dynamic platelet function tests, such as Rotational Thromboelastometry (ROTEM), and other conventional coagulation tests (44-48). In addition ten other studies specifically analyzed dynamic platelet function in terms of their prediction of mortality (49-51), prediction of transfusion requirements and mass transfusions (52-56) (**Table II**).

Diagnostics of acid-base changes

Between 2003 (57) and 2019, multiple studies have been performed assessing acid-base changes (58-62). The majority of these studies indicate an admission lactate level between 2.0 and 2.5mmol/l as a threshold. Two groups selected higher levels 3.0 mmol/l (63) and 4.0 mmol/l (64). The most recent study is a systematic review and the main results are shown in **Table III** (65). It becomes evident, that only one lactate measure is not reliable as a marker for defining the status of a patient (13), but more the clearance capacity of lactate (62, 66-69), (**Table III**).

Scoring systems to determine the timing of surgery

Six different recommendations have been available in the literature (all published later than 2005). Among them, four were deemed to be relevant and are depicted in **Table IV**.

Indications for surgery and their dependency on the severity of injury

Most of the studies that present with recommendations for surgical fixation of major fractures derive from single center analysis (**Table V**). Two publications were done on the basis of a trauma registry, one compares different indications in two centers and one study is an RCT in ten centers. **Table VI** summarized studies that use lactate and acid base changes as the main indicator for surgical decision making. There is a certain variability in the recommendations regarding the time and the threshold level of lactate. **Table VII** indicates factors that were described in the early stages of the development of staged surgical concepts, thus respecting injury severity and injury distributions. It provides an update on the parameters used today (e.g. replacement of a Swan Ganz catheter etc.) and an update on chest trauma scoring.

Part 2: Database analysis

Demographics

The database analysis includes 3668 patients. Most of the patients were male (n=2694, 73.4%). The mean ISS was 28.2 points (SD 15.1), mean NISS 37.2 points (SD 17.4). The average length of stay was 17.0 days (SD 18.7 days) with a mean length of ICU stay of 8.2 days (SD 10.5 days), and a mean ventilation time of 5.1 days (SD 8.1 days).

Demographic data are displayed in **Table VI**. Stratification was made into three different time periods, 867 patients (23.6%) of which were treated prior to 2002 (before introduction of damage control techniques (Group No DC)). Out of the remaining 2801 patients, 1262 (45.1%) patients belonged to the years 2003 and later (incorporation of damage control techniques for major fractures (Group DC)), and 1539 (54.9%) were treated after 2009 (changes in nonsurgical management, eg. transfusion and fluid management guidelines (Group DC Tr)).

Outcome Parameters

Patients were significantly older in Gr. DC Tr (43.2y ± 18.97y versus 49.6y ± 21.35y, $p<0.0001$) as a sign of increasing life expectancy. The mortality rate was significantly lower in group DC Tr (19.7%) when compared with group DC (32.7%, $p<0.0001$). Ventilation time decreased significantly (from 6.4days ± 8.6days to 3.61days ± 7.0days, $p<0.001$). Correspondingly the total ICU-stay decreased (9.4 ± 10.8 to 6.3days ± 9.1days, $p<0.001$). Further results regarding complications are graphically displayed in **Figure 1**.

DISCUSSION

Trauma continues to represent a major cause of severe illness in the working age population (70-72). In many societies, attempts have been undertaken to improve trauma care by implementation of trauma system availability (72, 73), certification strategies for hospital (74) and teaching tools (75).

Among the important physiological principles are the relevance of hypothermia, acidosis and coagulopathy in the trauma patient on admission (76).

Principles of physiologic factors

Multiple parameters are relevant in the management for the physiological changes after multiple injuries and they affect multiple disciplines including general surgeons, anesthesiologists, intensivists and orthopedic surgeons (77, 78).

It has also been confirmed that additional cofactors are crucial in determining the risk of complications. Included in these are severe prolonged hypotension, reperfusion injury and severe chest trauma (79, 80). Inflammatory mediators, such as interleukins have been used for monitoring patients pre-operatively and during the hospital stay (16, 81-84). This is in line with other results from the *"Inflammation and the host response to injury collaborative research program"*, which reinforces the relevance of numerous clinical inflammatory parameters and biomarkers for the prediction of clinical complications (14). However, their inclusion as a decision-making factor has been limited to certain trauma systems and is technically feasible in Level 1 trauma centers only (85). In this line, many centers that admit severely injured patients would not be able to differentiate between different phenotypes within the entirety of global clotting factor abnormalities (86).

Among other factors, the common language in treating these patients is important, and the definition of polytrauma is among them. Between 2006 and 2012, a consensus process took place, guided by members of multiple trauma societies, such as the European Society of Trauma and Emergency Surgery (ESTES), the American Association for the Surgery of Trauma (AAST), the Orthopaedic Trauma Association (OTA), and the German Trauma Society (DGU). Based on multiple discussions and a consensus process, the evidence based criteria to identify patients with increased mortality rates were found to be multifactorial: additionally to AIS the relevance of age, hypotension on admission, GCS on admission, and coagulopathy were identified as relevant risk factors for lethal outcome (87).

Principles of resuscitation

Since the 1980s, the credo of resuscitation was to provide *rapid and aggressive fluid replacement* to avoid any hypoperfusion and, if present, to restore perfusion as rapidly as possible (88). The concept was believed to be valid throughout the world and was applied both in civilian and military trauma management (89, 90). Thus, resuscitation with crystalloids and packed red blood cells (pRBCs) represented the standard treatment at the beginning of the millennium.

Later, *aggressive volume replacement* was discussed to be the *cause for increased bleeding* in acute life threatening conditions and reopening blood vessels was discussed to occur in association with it. Other disadvantages appeared to be mechanistic, such as an increase of hydrostatic pressure (91-93), decrease in body temperature induced by the volume influx, and subsequent dilutional coagulopathy (94, 95). Further adverse outcomes include increased rates of postoperative ileus, ARDS, abdominal compartment syndrome (ACS), cardiac decompensation, and infectious complications including surgical site and blood stream infections (96).

According to the current understanding, blood loss is increased with increased mean arterial pressure and dilution of clotting factors (97).Therefore, *permissive hypovolemia, and damage control resuscitation (DCR)* represent the reference treatment today (95, 98, 99). Among other factors, the reduction in dilutional effects by permissive hypovolemia is thought to enhance and improve clot formation (100).

Although multiple preclinical scoring systems have been described, the availability of systems for the early clinical stages have been sparse. Most of these have focused on the prediction of massive transfusion (101), or used parameters of hemorrhagic shock to describe the risk of complications (102). In contrast, Kutcher et al. recently suggested looking at coagulopathy in a more detailed fashion, as coagulopathic patients present with mixed risk factors, and coagulopathy has deleterious effects independent of injury severity, shock, and the vicious triad (103).

Management of coagulopathy

Up to 35% of patients with severe injuries present with a trauma-induced coagulopathy on admission (47). Abnormal coagulation tests are associated with higher mortality even in the moderately injured, suggesting that their importance may be underappreciated (104). In general, certain principles appear to be relevant in managing coagulopathy:

1. The efficacy of plasma repletion appears to play out in the first few hours of resuscitation
2. Blood volume deficit may be a more sensitive marker of efficacy in some populations
3. Early plasma replacement appears to prevent some patients from going on to require massive transfusion (105)

Platelet count on admission is a commonly used parameter, although it has not been proven useful to guide resuscitation. One of the few studies that deal with the course of the platelet count was published by Stansbury et al., where admission platelet count in critically injured patients was noticed to be normal in most cases and decreases within 24 hours. Low platelet counts at admission and over a further period of days were strongly associated with increased mortality (106). Other authors compared measurement of Factor V, protein C activity, and anti-thrombin III on-scene to in hospital levels. It was found that patients showed parameters to be 60% of normal on hospital admission and trending towards a worsening degree of coagulopathy compared to on-scene, until specific therapy was initiated (107).

The standard parameters to diagnose coagulopathy around the change of the millennium appeared to be INR and platelet count (108). These measures have been incorporated into existing guidelines, despite an obvious lack of evidence (109, 110). It is known that many standard coagulation tests require long turnaround times, i.e. for separation of plasma from red cells that provide information solely of the initial phases of clot formation (111). Further, these tests were developed for congenital bleeding disorders, and their precise role in guiding transfusion therapy in trauma has not been validated (112). Therefore, in addition to platelet counts, multiple dynamic test systems have been developed to rapidly identify these patients including the critical administration threshold (CAT), the assessment of blood consumption (ABC) score, and other dynamic platelet function tests (*diamond of death*) as identified by thrombelastography (TEG). These tests have been recommended in various studies (7, 113-118), while other studies found no evidence for benefit using TEG and ROTEM (119).

Although they were discussed to be user dependent, this category appears to improve, as new devices become available. Likewise, it was recently emphasized that multiple injured patients present with a spectrum of post injury fibrinolysis, possibly identifiable by both rTEG and ROTEM. Citrated rTEG is a quick and effective method to guide hemostatic resuscitation in trauma patients and does not perform inferiorly to the citrated native of citrated kaolin TEG despite the addition of activation factors (52, 120). TEG and ROTEM provide some agreement in their ability to derive fibrinolysis phenotypes to stratify patients into different risk groups. Of note, this information is in view of inclusion of different other variables such as INR, PTT, platelet count, fibrinogen, D-Dimer, etc. (121).

Published Guidelines

Several guidelines for coagulopathy have been published since 2005 (122). Among them is a European guideline, which is renewed on a regular basis (109, 123, 124). Medication for hemorrhage appears to increase Plasma-Platelet-RBC ratios, which were shown to be associated with improved outcome in 466 massively transfused civilian trauma patients (125). It was therefore debated whether the 1:1 ratio of Fresh Frozen Plasma may be indicated in life threatening post injury coagulopathy (126). Some suggest that the critical threshold for survival in civilian patients sustaining post injury life threatening coagulopathy may be in the range of 1:2-3 FFP:pRBCs, as the lowest predictive probability of mortality of 0.2 to 0.3 is the case. Albeit, the use of massive amounts of FFP, ARDS rates are not affected (127).

The common definition of *massive transfusion* (10 units RBCs per 24 hours) has been *changed to 10 units RBCs per 6 hours* to better reflect the dominant time period of the acute hemorrhagic event, as well as the associated physiologic consequences. Meanwhile, *goal directed therapy* represents the current standard (128, 129). Along with these changes, the use of additional medication such as Tranexamic acid (TXA) have been shown to be important in acute hemorrhage conditions; some suggest an enhancement of clot formation (130), a group of patients presenting with depletion of fibrinolysis treated with TXA to develop a significantly improved fibrin clot strength (117, 131-135).

Importance of Acid Base changes

There is a long and significant history regarding patient assessment using acid base changes (136, 137). Likewise, the development of the calculation of lactate clearance dated back to the early 1960s, where an improved lactate value was calculated as percentage change of initial lactate value and secondary lactate value: $\frac{(Il-DL)}{IL} \times 100\%$ (136). Since then, various authors have looked at issues of resuscitation based upon changes in pH, lactate and base excess (BE) (138-140). In 2012, a time correction was added and the percentage clearance per hour was described (143). Four categories were developed based upon lactate level and the threshold of 2.5mmol/l: IL and DL ≤ 2.5; IL > 2.5 and DL ≤ 2.5; IL ≤ 2.5 and DL > 2.5; IL + DL > 2.5 and appear to be indicative of early hemorrhage induced mortality (144).

Acid-Base changes appear to play an important role in the management of resuscitation and prediction of complications. It has been applied for prehospital assessment of trauma patients, usually to predict complications and mortality (141). Admission lactate has been used to predict sepsis, especially in the presence of substantial initial hemorrhage (142).

To our knowledge, the first publication to use the term "lactate clearance" looked at lactate measures at 8, 16, 24, 36, and 48 hours after injury; the threshold level was set at 2mmol/l, comparable to other authors (**Table III**). They concluded a survival rate of 75% after normalization of lactate levels between 24 and 48 hours (145). Nevertheless, the differentiation of arterial and venous blood gas analysis (BGA) remains important. This was believed to be rather reliable for many years (146), until a recent systematic review described hyperlactemia with rather poor agreement between arterial and venous BGA. The authors further concluded that a threshold level of 2.0 mmol/l for screening and arterial BGA for confirms hyperlactemia (147). Several authors defined differing threshold levels depending on their research question (**Table III**), the most commonly used threshold level being between 2.0 and 2.5 mmol/l (143).

Dezman et al. investigated the relevance of elevated lactate levels in trauma patients upon admission. They summarized patients treated between 2010 and 2012 with an admission lactate level of >3mmol/l. Patients were included who had two lactate measures within 24 hours: Group 1 normalized lactate within 24 hours (high clearance), and Group 2 without improvement of lactate level within 24 hours (poor clearance). Based on this methodology, they concluded a superiority of 24 hour lactate clearance compared to initial lactate value (63, 148). Each group included about 25% penetrating injuries. In Group 1 (high clearance), the initial blood pressure and the associated heart rate were substantially better compared to Group 2 (poor clearance). Therefore, it is important to consider their exclusion criteria: patients without lactate measurements within 24 hours, patients that were transferred to the trauma center, or those who died within 15 minutes of arrival. In the vast majority of included patients, the lactate level was not elevated.

Failed lactate clearance is associated with increased mortality. The majority of authors set a threshold level of *lactate between 2.0 and 2.5 mmol/l*. Higher threshold levels were only used by two authors (**Table III**) (63, 149). Further, it is unclear whether arterial or venous levels should be utilized. A clear difference between both approaches has not yet been proven. In the interpretation of lactate level, certain preexisting conditions have to be considered: alcohol consumption (150), chronic renal failure, metabolic diseases (151), medication, sepsis, seizures, CO-poisoning, strenuous exercise, and respiratory or hepatic failure all influence baseline lactate levels and lactate clearance (152, 153). Therefore, we feel that sole use of lactate value to guide management in polytrauma patients may be dangerous and is not advisable.

Early prediction of complications

Prediction of outcomes after injury is traditionally based upon injury severity and stratification thereof. To improve the mere anatomic-based outcome model, physiologic changes and measures for shock were added (87). A single center study described a prediction model for mortality with the main weight on GCS (22%), followed by BE (8%), requirement of blood transfusion (8%), ISS (5%), and age (4%). This model had a 63% sensitivity, and a 94% specificity (ROC 0.96) (154). Our group developed an easy to use and reliable score to allow stratification of multiple injured patients and allow safe definitive fixation in stable patients (155). The ONPOINT study group investigated an automated analysis of pulse oximetry signals and laboratory values. They used automated analysis of triage vital signs during 15minutes of pulse oximetry signals. Laboratory values predicted the use of blood transfusion during trauma resuscitation (156). The authors discussed automated calculations from a noninvasive vital sign monitor interfaced with a point-of-care laboratory device to support clinical decisions by recognizing patients in need of transfusion. These features improve prediction of early mortality compared to heart rate and systolic blood pressure (shock index) alone (157).

Ultrasound was discussed as equally useful as laboratory testing as a measure of volume responsiveness in trauma patients by monitoring the vena cava and adjacent structures (158). In a clinically relevant heterogeneous population, ultrasound was only moderately predictive of volume resuscitation requirements whereas the change in diameter of the inferior vena cava was not found to be predictive.

Based on a survey in 2013, the 48 - hour ventilation period has been found to be predictive for complications (159). Patients that developed complications had a lower initial GCS and lower ISS. Further, lung contusion and ventilation duration more than 48 hours were associated with development of further complications (159).

Scoring of the trauma patient for the management of orthopaedic injuries

Over the last two decades, six different scoring systems have been published that attempt to deal with treatment strategies for multiple injured patients (64, 80, 101, 155, 159, 160). Both scoring methods published by Dienstknecht (159) and Ogura (101) require extended observation times (48 hours) for completion and were not deemed to be feasible for clinical use in the acute phase.

The remaining four scoring systems show considerable differences that appear to depend upon the initial research question that led to the development of the given score. The overall goal was to stratify injured patients to give treatment recommendations, but the methodology and the included variables differ substantially (**Table IV**). The initial grading system was published in 2005 and it summarized numerous parameters published by various authors. Subsequently, modifications were made based on the availability of the local data base. The modifications included the omission of Factor II and V, fibrinogen, D-Dimer levels, the Advanced Trauma Life Support (ATLS) classification for shock, urinary output, the PaO_2/FiO_2 ratio, and the Thoracic Trauma Score (160). Furthermore, patients without chest trauma were included, the threshold values of lactate were changed and the frequency of pRBCs administered were lowered. The resulting scale was named mCGS (modified clinical grading scale), as the authors used the term Clinical Grading Scale, as the parameters published in 2005 lacked a name. These modifications resulted in a poorer predictive capability of the mCGS compared to the scale published in 2005. The modifications induce a selection bias towards a population that has a different risk profile for systemic complications and is therefore not comparable with the original recommendation (161).

The development of the early appropriate care (EAC) protocol aimed to identify patients cleared for definitive surgery. It uses admission lactate with a threshold level of 4 mmol/L, below which patients are thought to be cleared for any major surgery.

The Polytrauma Grading Score (PTGS) was developed based on clinical and laboratory parameters on patient admission. Patients were later stratified according to mortality rate. The stratification leads to either stable, borderline, unstable or in extremis patients. The management strategies are based upon the strata of the multiple injured patient.

Recommendation guidelines for orthopedic injuries in polytrauma

The controversies in the literature regarding timing of definitive fracture fixation for polytrauma patients is ongoing. Much has been learned from those authors that appear to perform early definitive stabilization in almost any patient versus those that have been accused of delaying definitive fracture care. Options regarding geographic, or trauma system related differences were displayed in a matched paired analysis including patients treated in the United States and patients treated in Europe and revealed comparable timing of fracture fixation despite different trauma systems (162).

As indicated in **Table V**, most authors appear to respect the injury severity of a given population of polytrauma patients and split their recommendations towards either early definitive or early temporary fracture fixation. Because of this, patients with higher ISS are less likely to be treated with early definitive fracture fixation. This trend is independent of the general conclusion of the given publication, and independent of the general use of damage control strategies (163). Moreover, authors that favor early definitive stabilization in all patients have a considerable number of patients with nonoperative management of the major fracture (164), or place patients with initial external fixation into the late fixation group (64), affecting the results and the conclusions.

Historical Background of published recommendations (table VIII)

Early Total Care (ETC)

This concept was coined by various authors and was made popular by many authors, given the fact that the rule used to be not to treat major fractures due to the fear of fat embolism. Bone and Johnson published the first randomized controlled study on this subject and proved that early fixation of isolated fractures and a group of multiply injured patients was beneficial (165). They performed definitive fixation of major extremity fractures within 24 hours after patient admission. The simplified focus of the study attributed fractures of long bones to ARDS and the aim was to reduce pulmonary complications, as ARDS represented the most important complication. Patients included in their study were less severely injured compared to patients in subsequent studies. They included 95 isolated femur fractures and 83 multiple injured patients, less than half of which (40 patients) had indication for ventilation. Further, the authors used the Hospital Trauma Index to calculate the ISS, which also provides higher values compared to the AIS (166, 167).

Damage Control Orthopaedics (DCO)

This concept was first described by Scalea in 2000 (168), and appeared to be relevant, as an increasing number of patients were recognized to leave operating rooms in compromised conditions after prolonged early surgeries (169). Additionally, certain aspects of initial injury types were observed to imply a special risk for secondary complications including SIRS, MOF, sepsis, or ARDS. With DCO treatment, the survival and the rate of complications was improved (170-175). This observation was supported by a prospective randomized study that showed a reduction of acult lung injuries in borderline patients (12), two supportive trauma registry analyses from the NTDB and Tr_DGU, and a matched pair analysis (162).As a result damage control orthopedics appears to represent a feasible option for patients at special risk and has been applied worldwide, independent of trauma center, geographic or treatment differences (174, 176-181).

Early Appropriate Care (EAC)

More recently, emphasis was placed on elevated lactate levels with the similar background, i.e. to all stabilize fractures definitively, whenever lactate stabilizes. It was developed in a retrospective data base and suggests performing definitive stabilization of all major fractures, when lactate levels decrease. It is thus similar to ETC (64).

Safe Definitive Surgery (SDS)

This concept was developed to refine DCO strategies and avoid overzealous use of external fixation "for convenience". Thus, it attempted to describe steps to separate patients at special risk to develop complications over time (182). SDS uses easily available routine clinical parameters and reflects upon the overall injury severity and distribution of injuries as a basis to understand the dynamic clinical changes that may ensue within hours after injury. It includes criteria for completion of resuscitation at the end of the trauma bay period (183). The continual reassessment of patients at risk is a crucial factor and is suggested to be performed multiple times, i.e. after completion of resuscitation, after completion of a major surgical step in planned staged management of fractures and prior to surgery in the ICU (161).

Prompt Individualized Safe Management (PRISM)

This is a concept that encompasses injury mechanism and distribution, ATLS protocols, physiological state, early diagnostics, and the patient response. The individualized approach includes patient age, gender, co-morbidities and special aspects that may cause management changes, such as pregnancy. In addition to the previous recommendations, it reflects upon local resources both in terms of manpower and hospital capacity. Moreover, this tactic overcomes previous dogma, (such as the "window of opportunity" for certain major fracture fixations) by not recommending setting time limits for initiation of surgery. It therefore respects recent advances in patient assessment using inflammatory mediators and allows one to perform intra-operative reassessments. The authors describe it as representing a philosophy of "doing no further harm" in patients with multiple injuries in order to achieve the best possible outcome in a given patient, hospital, and trauma system environment (184). It may be supported by the fact that complication rates are similar despite treatment in different trauma centers, when staged surgical management of major fractures is performed (162).

Certain criteria about the published treatment guidelines and protocols are summarized in table VIII.

Current risk factor assessment and integration into the results from a level I trauma center

In the current literature, multiple new factors have been summarized and they appear to consist of factors caused by the initial trauma (static), which can then be modified rapidly (dynamic) by rescue conditions, treatment strategies (management of resuscitation, massive transfusion, surgical strategies and perioperative care).

As far as blunt chest trauma is concerned, the most recent literature forecasts the following:

The availability of scoring systems regarding chest trauma has improved the prediction of complications and may be worth considering (185). Specifically, the thoracic trauma score has been shown to be equal or even superior to other scoring systems. It might serve as a predictor of pulmonary failure and also is more precise compared to the AIS thoracic alone (186-188).

Although it has been speculated that the incidence of ARDS has declined and its importance in the survival after trauma has declined, this effect has not been confirmed in recent trauma studies. A systematic review and meta-analysis showed no trend in the incidence of trauma-induced ARDS across the last three decades. There was no significant geographical difference in the incidence of posttraumatic ARDS (comparing United States 13.4% and Europe 12.5%) (79).

It has been argued that the importance of pulmonary failure has declined substantially and acute lung injury (ALI) as a separate entity should be erased; still it continues to be assessed in the literature (189, 190). Certain risk factors were found to be predictive as follows - while blood and plasma transfusion were not independently associated with ARDS, platelet transfusion was a significant independent risk factor. The role of platelets may be explained mechanistically by lung injury models of pulmonary platelet sequestration with peripheral thrombocytopenia. This warrants further investigation (191, 192).

The patient at risk (borderline condition) can be refined as follows - prior to the presentation of the damage control concept, general surgeons implemented the concept of limiting the amount and the duration of the initial operation in a bleeding trauma patient suffering from the triad of death (76, 168, 193). The identification of the patient at risk implies multiple parameters including an ISS > 40 points, multiple injuries in association with thoracic trauma (AIS thoracic > 2), multiple injuries with severe abdominal or pelvic injury, hemorrhagic shock, bilateral major long bone fractures, additional head injury (AIS head > 3) (194). Some of these criteria continue to be of value, and new recommendations are summarized in **Table IX** (195). The timing of operations is recognized as a risk factor for complications and overzealous surgeries are described to be potentially detrimental in patients at risk (196). Likewise, it is confirmed that delayed fracture fixation in the more stable patients is disadvantageous and associated with an increased rate of pulmonary complications (12).

In this line, it is interesting to differentiate between those polytrauma patients that 1) receive treatment within 72 hours that develop complications and major hemorrhage after admission with eventual death and 2) those that develop late complications and mortality. In this line, lactate appears to be a predictor of early death while multiple other parameters appear to predict late death. Our data base analysis has tried to incorporate both, early and late mortality rates. The results obtained in an analysis of 3668 polytrauma patients reveals that the changes in surgical management was associated with improvements in mortality rates and outcomes (comparison between the outcomes before 2002 (Group No DC) versus 2003-2008 (Group DC), (**Figure 1**). It appears to be relevant for both early and late complications. Subsequently, implementation of protocols of massive transfusion and volume treatment was associated with further improvements in all factors, early and late mortality rates and even for late complication rates (Group DC) versus patient treated after changes in the transfusion and resuscitation management (2009 and later, Group DC Tr), (**Figure 1**). The same was found in a subgroup analysis published by Stein et al. (9). The authors compared two time periods before and after implementation of transfusion guidelines. Their changes were summarized as follows: In 2005–2007, the observed and trauma associated severe hemorrhage score that predicted the incidence of massive transfusion were identical. Whereas in 2012–2014, the observed incidence was less than half that predicted (3.7% vs. 7.5%) and was also proven for red blood cells and fresh frozen plasma.

We are aware of certain limitations apply, as the inclusion of patients with other than orthopedic injuries may have had an effect (inclusion of head trauma patients may interfere with some of the results obtained). Also, one may argue that the treatment of patients before the introduction of balanced surgical tactics may have been critical. However, we aimed at performing a survey on patients treated at time frames of other published data bases, dealing with the same topic (64).

We therefore feel that our data are relevant and supportive of the literature review performed. Interestingly, the striking improvements in outcomes in both time periods occurred in the absence of any other sustained management changes, such as the trauma system, rescue times, patient age, or incidences of chest trauma.

CONCLUSION

In response to the questions addressed in the introduction, we draw the following conclusions:

Resuscitation has changed towards permissive hypovolemia tactics in selected patients. Massive transfusion protocols have been developed and lead to improvement in survival rates. Several management protocols have been developed for the management of major fractures. Validation of any of these protocols is not available to date and should be performed. A patient tailored treatment – individualized medicine approach - is desirable and should cover several pathogenetic pathways to avoid errors described in the current manuscript. Among the existing ones, the PRISM approach appears to be most comprehensive, as it covers issues of rescue, trauma system environment, logistics, and multiple patient factors including patient outcome.

A staged surgical approach has replaced the approach of trying to stabilize all fractures within 24 hours after injury. Obviously, damage control should be limited to those patients at risk, not as an excuse to delay definitive fixation in stable patients "for convenience". In stable patients, fractures are stabilized as early as possible, based on individual patient physiology rather than a "window of opportunity". Validation of trauma protocols is required, or development of new ones in the future.

In summary, various innovations have occurred since the turn of the millennium and they have helped evaluate the trauma patient with multiple injuries. Among these, we have identified four major areas: 1) Emergency room management has moved towards a strategy of permissive hypovolemia and point of care testing; 2) The continual reassessment of the trauma patient after resuscitation has become more standardized and involves endpoints of coagulopathy and acid base changes; 3) The criteria to assess borderline patients and those at special risk have been refined; 4) Scoring systems and scales have been described that may help guide the management of patients that may benefit from damage control versus for safe definitive early surgery for major fractures.

Funding: No external funding was used for this study

Conflict of interest: None of the authors have any conflicts of interest to declare

Ethical considerations: According to the ethical committee, there is no need for approval for literature reviews. The database analysis was approved by the local institutional review board (IRB) according to IRC guidelines (No. St. V. 01-2008)

REFERENCES

1. Scalea TM, Boswell SA, Scott JD, Mitchell KA, Kramer ME, Pollak AN. External fixation as a bridge to intramedullary nailing for patients with multiple injuries and with femur fractures: damage control orthopedics. Journal of Trauma and Acute Care Surgery. 2000;48(4):613-23.
2. Andruszkow H, Haasper C, Lob G, Pfeifer R, Stengel D, Hildebrand F, et al. Status of Road Safety and Injury Burden: Europe. Journal of Orthopaedic Trauma. 2014;28:S39-S40.
3. Buzeman DG, Viano DC, Lovsund P. Car occupant safety in frontal crashes: A parameter study of vehicle mass, impact speed, and inherent vehicle protection. Accident Analysis and Prevention. 1998;30(6):713-22.
4. Richter M, Krettek C, Otte D, Wiese B, Stalp M, Ernst S, et al. Correlation between crash severity, injury severity, and clinical course in car occupants with thoracic trauma: A technical and medical study. Journal of Trauma-Injury Infection and Critical Care. 2001;51(1):10-6.
5. Fredriksson R, Shin J, Untaroiu CD. Potential of Pedestrian Protection Systems-A Parameter Study Using Finite Element Models of Pedestrian Dummy and Generic Passenger Vehicles. Traffic Injury Prevention. 2011;12(4):398-411.
6. Woodford MR, Mackenzie CF, DuBose J, Hu P, Kufera J, Hu EZ, et al. Continuously recorded oxygen saturation and heart rate during prehospital transport outperform initial measurement in prediction of mortality after trauma. Journal of Trauma and Acute Care Surgery. 2012;72(4):1006-11.
7. Stein P, Studt JD, Albrecht R, Muller S, von Ow D, Fischer S, et al. The Impact of Prehospital Tranexamic Acid on Blood Coagulation in Trauma Patients. Anesthesia and Analgesia. 2018;126(2):522-9.
8. Meybohm P, Richards T, Isbister J, Hofmann A, Shander A, Goodnough LT, et al. Patient Blood Management Bundles to facilitate implementation. Anasthesiologie & Intensivmedizin. 2017;58:16-29.
9. Stein P, Kaserer A, Sprengel K, Wanner G, Seifert B, Theusinger O, et al. Change of transfusion and treatment paradigm in major trauma patients. Anaesthesia. 2017;72(11):1317-26.
10. Scalea TM, DuBose J, Moore EE, West M, Moore FA, McIntyre R, et al. Western Trauma Association Critical Decisions in Trauma: Management of the mangled extremity. Journal of Trauma and Acute Care Surgery. 2012;72(1):86-93.
11. Shah KJ, Chiu WC, Scalea TM, Carlson DE. Detrimental effects of rapid fluid resuscitation on hepatocellular function and survival after hemorrhagic shock. Shock. 2002;18(3):242-7.
12. Pape HC, Rixen D, Morley J, Husebye EE, Mueller M, Dumont C, et al. Impact of the method of initial stabilization for femoral shaft fractures in patients with multiple injuries at risk for complications (borderline patients). Annals of Surgery. 2007;246(3):491-501.
13. Pape HC, Giannoudis PV, Krettek C, Trentz O. Timing of fixation of major fractures in blunt polytrauma: role of conventional indicators in clinical decision making. J Orthop Trauma. 2005;19(8):551-62.
14. Sauaia A, Moore EE, Johnson JL, Chin TL, Banerjee A, Sperry JL, et al. Temporal trends of postinjury multiple-organ failure: still resource intensive, morbid, and lethal. The journal of trauma and acute care surgery. 2014;76(3):582.
15. Bazhin AV, Egorova EA. Diagnostic Imaging in Patients with Spinal Injury: an Optimized Procedure Based on Novel Technologies. Sovremennye Tehnologii V Medicine. 2018;10(2):125-33.
16. Giannoudis PV, Harwood PJ, Loughenbury P, Van Griensven M, Krettek C, Pape HC. Correlation between IL-6 levels and the systemic inflammatory response score: Can an IL-6 cutoff predict a SIRS state? Journal of Trauma-Injury Infection and Critical Care. 2008;65(3):646-52.
17. Grunherz L, Jensen KO, Neuhaus V, Mica L, Werner CML, Ciritsis B, et al. Early computed tomography or focused assessment with sonography in abdominal trauma: what are the leading opinions? European Journal of Trauma and Emergency Surgery. 2018;44(1):3-8.

18. Dar GN, Tak SR, Kangoo KA, Dar FA, Ahmed ST. External fixation followed by delayed interlocking intramedullary nailing in high velocity gunshot wounds of the femur. Ulusal Travma Ve Acil Cerrahi Dergisi-Turkish Journal of Trauma & Emergency Surgery. 2009;15(6):553-8.
19. Egol KA, Tejwani NC, Capla EL, Wolinsky PL, Koval KJ. Staged management of high-energy proximal tibia fractures (OTA types 41): the results of a prospective, standardized protocol. Journal of orthopaedic trauma. 2005;19(7):448–55.
20. Mehta S, Mirza AJ, Dunbar RP, Barei DP, Benirschke SK. A Staged Treatment Plan for the Management of Type II and Type IIIA Open Calcaneus Fractures. Journal of Orthopaedic Trauma. 2010;24(3):142-7.
21. Sirkin M, Sanders R, DiPasquale T, Herscovici D. A staged protocol for soft tissue management in the treatment of complex pilon fractures. J Orthop Trauma. 2004;18(8 Suppl):S32-8.
22. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, et al. The European guideline on management of major bleeding and coagulopathy following trauma. 2016;20(1):100.
23. Roberts DJ, Bobrovitz N, Zygun DA, Ball CG, Kirkpatrick AW, Faris PD, et al. Indications for Use of Damage Control Surgery in Civilian Trauma Patients: A Content Analysis and Expert Appropriateness Rating Study. Ann Surg. 2016;263(5):1018-27.
24. Haan JM, Biffl W, Knudson MM, Davis KA, Oka T, Majercik S, et al. Splenic embolization revisited: A multicenter review. Journal of Trauma-Injury Infection and Critical Care. 2004;56(3):542-7.
25. Haan JM, Bochicchio GV, Kramer N, Scalea TM. Nonoperative management of blunt splenic injury: A 5-year experience. Journal of Trauma-Injury Infection and Critical Care. 2005;58(3):492-8.
26. Leenen LP. Abdominal trauma: from operative to nonoperative management. Injury. 2009;40 Suppl 4:S62-8.
27. Sartorelli KH, Frumiento C, Rogers FB, Osler TM. Nonoperative management of hepatic, splenic, and renal injuries in adults with multiple injuries. Journal of Trauma-Injury Infection and Critical Care. 2000;49(1):56-61.
28. Glass NE, Burlew CC, Hahnhaussen J, Weckbach S, Pieracci FM, Moore EE, et al. Early Definitive Fracture Fixation is Safely Performed in the Presence of an Open Abdomen in Multiply Injured Patients. Journal of Orthopaedic Trauma. 2017;31(12):624-30.
29. Cotton BA, Reddy N, Hatch QM, LeFebvre E, Wade CE, Kozar RA, et al. Damage Control Resuscitation Is Associated With a Reduction in Resuscitation Volumes and Improvement in Survival in 390 Damage Control Laparotomy Patients. Annals of Surgery. 2011;254(4):598-605.
30. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015;4.
31. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (MINORS): Development and validation of a new instrument. Anz Journal of Surgery. 2003;73(9):712-6.
32. Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj-British Medical Journal. 2011;343:9.
33. Pape H-C, Giannoudis P, Krettek C. The timing of fracture treatment in polytrauma patients: relevance of damage control orthopedic surgery. The American journal of surgery. 2002;183(6):622–9.
34. Spahn DR, Moch H, Hofmann A, Isbister JP. Patient Blood Management The Pragmatic Solution for the Problems with Blood Transfusions. Anesthesiology. 2008;109(6):951-3.
35. Gonzalez EA, Moore FA, Holcomb JB, Miller CC, Kozar RA, Todd SR, et al. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. Journal of Trauma-Injury Infection and Critical Care. 2007;62(1):112-9.

36. Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: Impact on in-hospital mortality. Journal of Trauma-Injury Infection and Critical Care. 2002;52(6):1141-6.
37. Duchesne JC, Kimonis K, Marr AB, Rennie KV, Wahl G, Wells JE, et al. Damage Control Resuscitation in Combination With Damage Control Laparotomy: A Survival Advantage. Journal of Trauma-Injury Infection and Critical Care. 2010;69(1):46-52.
38. Duchesne JC, McSwain NE, Cotton BA, Hunt JP, Dellavolpe J, Lafaro K, et al. Damage Control Resuscitation: The New Face of Damage Control. Journal of Trauma-Injury Infection and Critical Care. 2010;69(4):976-90.
39. Duchesne JC, Kaplan LJ, Balogh ZJ, Malbrain M. Role of permissive hypotension, hypertonic resuscitation and the global increased permeability syndrome in patients with severe haemorrhage: adjuncts to damage control resuscitation to prevent intra-abdominal hypertension. Anaesthesiology Intensive Therapy. 2015;47(2):143-55.
40. Baraniuk S, Tilley BC, del Junco DJ, Fox EE, van Belle G, Wade CE, et al. Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) Trial: Design, rationale and implementation. Injury-International Journal of the Care of the Injured. 2014;45(9):1287-95.
41. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma The PROPPR Randomized Clinical Trial. Jama-Journal of the American Medical Association. 2015;313(5):471-82.
42. Meyer DE, Cotton BA, Fox EE, Stein D, Holcomb JB, Cohen M, et al. A comparison of resuscitation intensity and critical administration threshold in predicting early mortality among bleeding patients: A multicenter validation in 680 major transfusion patients. Journal of Trauma and Acute Care Surgery. 2018;85(4):691-6.
43. Robinson BRH, Cohen MJ, Holcomb JB, Pritts TA, Gomaa D, Fox EE, et al. RISK FACTORS FOR THE DEVELOPMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME FOLLOWING HEMORRHAGE. Shock. 2018;50(3):258-64.
44. Lier H, Krep H, Schochl H. Coagulation management in the treatment of multiple trauma. Anaesthesist. 2009;58(10):1010-+.
45. Spahn DR, Bouillon B, Cerny V, Duranteau J, Filipescu D, Hunt BJ, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. Critical Care. 2019;23:74.
46. Rugeri L, Levrat A, David JS, Delecroix E, Floccard B, Gros A, et al. Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. Journal of Thrombosis and Haemostasis. 2007;5(2):289-95.
47. Holcomb JB, Minei KM, Scerbo ML, Radwan ZA, Wade CE, Kozar RA, et al. Admission Rapid Thrombelastography Can Replace Conventional Coagulation Tests in the Emergency Department Experience With 1974 Consecutive Trauma Patients. Annals of Surgery. 2012;256(3):476-86.
48. Veigas PV, Callum J, Rizoli S, Nascimento B, da Luz LT. A systematic review on the rotational thrombelastometry (ROTEM (R)) values for the diagnosis of coagulopathy, prediction and guidance of blood transfusion and prediction of mortality in trauma patients. Scandinavian Journal of Trauma Resuscitation & Emergency Medicine. 2016;24:14.
49. Levrat A, Gros A, Rugeri L, Inaba K, Floccard B, Negrier C, et al. Evaluation of rotation thrombelastography for the diagnosis of hyperfibrinolysis in trauma patients. British Journal of Anaesthesia. 2008;100(6):792-7.
50. Schochl H, Cadamuro J, Seidl S, Franz A, Solomon C, Schlimp CJ, et al. Hyperfibrinolysis is common in out-of-hospital cardiac arrest Results from a prospective observational thromboelastometry study. Resuscitation. 2013;84(4):454-9.
51. Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. Journal of Thrombosis and Haemostasis. 2012;10(7):1342-51.

52. Leemann H, Lustenberger T, Talving P, Kobayashi L, Bukur M, Brenni M, et al. The Role of Rotation Thromboelastometry in Early Prediction of Massive Transfusion. Journal of Trauma-Injury Infection and Critical Care. 2010;69(6):1403-8.
53. Tauber H, Innerhofer P, Breitkopf R, Westermann I, Beer R, El Attal R, et al. Prevalence and impact of abnormal ROTEM (R) assays in severe blunt trauma: results of the 'Diagnosis and Treatment of Trauma-Induced Coagulopathy (DIA-TRE-TIC) study'. British Journal of Anaesthesia. 2011;107(3):378-87.
54. Schochl H, Solomon C, Traintinger S, Nienaber U, Tacacs-Tolnai A, Windhofer C, et al. Thromboelastometric (ROTEM) Findings in Patients Suffering from Isolated Severe Traumatic Brain Injury. Journal of Neurotrauma. 2011;28(10):2033-41.
55. Davenport R, Manson J, De'Ath H, Platton S, Coates A, Allard S, et al. Functional definition and characterization of acute traumatic coagulopathy. Critical Care Medicine. 2011;39(12):2652-8.
56. Hagemo JS, Christiaans SC, Stanworth SJ, Brohi K, Johansson PI, Goslings JC, et al. Detection of acute traumatic coagulopathy and massive transfusion requirements by means of rotational thromboelastometry: an international prospective validation study. Critical Care. 2015;19:7.
57. Kaplan LJ, Frangos S. Clinical review: Acid-base abnormalities in the intensive care unit. Critical Care. 2005;9(2):198-203.
58. Bedreag OH, Rogobete AF, Dumache R, Sarandan M, Cradigati AC, Papurica M, et al. Use of circulating microRNAs as biomarkers in critically ill polytrauma patients. Biomarkers and Genomic Medicine. 2015;7(4):131-8.
59. Peñasco Y, González-Castro A, Rodríguez-Borregán JC, Llorca J. Base excess, a useful marker in the prognosis of chest trauma in the geriatric population. Rev Esp Anestesiol Reanim. 2017;64(5):250-6.
60. Piper GL, Kaplan LJ. Fluid and Electrolyte Management for the Surgical Patient. Surgical Clinics of North America. 2012;92(2):189-+.
61. Hernandez G, Ospina-Tascon GA, Damiani LP, Estenssoro E, Dubin A, Hurtado J, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock The ANDROMEDA-SHOCK Randomized Clinical Trial. Jama-Journal of the American Medical Association. 2019;321(7):654-64.
62. Drolz A, Horvatits T, Rutter K, Landahl F, Roedl K, Meersseman P, et al. Lactate Improves Prediction of Short-Term Mortality in Critically Ill Patients With Cirrhosis: A Multinational Study. Hepatology. 2019;69(1):258-69.
63. Dezman ZDW, Comer AC, Smith GS, Narayan M, Scalea TM, Hirshon JM. Failure to clear elevated lactate predicts 24-hour mortality in trauma patients. Journal of Trauma and Acute Care Surgery. 2015;79(4):580-5.
64. Vallier HA, Wang X, Moore TA, Wilber JH, Como JJ. Timing of orthopaedic surgery in multiple trauma patients: development of a protocol for early appropriate care. Journal of orthopaedic trauma. 2013;27(10):543-51.
65. van Tienhoven AJ, van Beers CAJ, Siegert CEH. Agreement between arterial and peripheral venous lactate levels in the ED: A systematic review. American Journal of Emergency Medicine. 2019;37(4):746-50.
66. Ayad M, Karanth S, Patel B. Lactate Levels at 6 Hrs. Is More Prognostic of in Hospital Mortality than A >=50 percnt Lactate Clearance in Severe Sepsis. American Journal of Respiratory and Critical Care Medicine. 2019;199.
67. Aramburo A, Todd J, George EC, Kiguli S, Olupot-Olupot P, Opoka RO, et al. Lactate clearance as a prognostic marker of mortality in severely ill febrile children in East Africa. Bmc Medicine. 2018;16.
68. Ryoo SM, Lee J, Lee YS, Lee JH, Lim KS, Huh JW, et al. Lactate Level Versus Lactate Clearance for Predicting Mortality in Patients With Septic Shock Defined by Sepsis-3. Critical Care Medicine. 2018;46(6):E489-E95.

69. Dekker SE, de Vries HM, Lubbers WD, de Ven PMV, Toor EJ, Bloemers FW, et al. Lactate clearance metrics are not superior to initial lactate in predicting mortality in trauma. European Journal of Trauma and Emergency Surgery. 2017;43(6):841-51.
70. Hyder AA, Wunderlich CA, Puvanachandra P, Gururaj G, Kobusingye OC. The impact of traumatic brain injuries: A global perspective. Neurorehabilitation. 2007;22(5):341-53.
71. Naghavi M, Abajobir AA, Abbafati C, Abbas KM, Abd-Allah F, Abera SF, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1151-210.
72. Mock C, Joshipura M, Arreola-Risa C, Quansah R. An Estimate of the Number of Lives that Could be Saved through Improvements in Trauma Care Globally. World Journal of Surgery. 2012;36(5):959-63.
73. Mock C, Quansah R, Krishnan R, Arreola-Risa C, Rivara F. Strengthening the prevention and care of injuries worldwide. Lancet. 2004;363(9427):2172-9.
74. Hirshberg A, Holcomb JB, Mattox KL. Hospital trauma care in multiple-casualty incidents: A critical view. Annals of Emergency Medicine. 2001;37(6):647-52.
75. Mohammad A, Branicki F, Abu-Zidan F. Educational and Clinical Impact of Advanced Trauma Life Support (ATLS) Courses: A Systematic Review. World Journal of Surgery. 2014;38(2):322-9.
76. Rotondo MF, Schwab CW, McGonigal MD, Phillips GR, Fruchterman TM, Kauder DR, et al. DAMAGE CONTROL - AN APPROACH FOR IMPROVED SURVIVAL IN EXSANGUINATING PENETRATING ABDOMINAL INJURY. Journal of Trauma-Injury Infection and Critical Care. 1993;35(3):375-83.
77. Keel M, Trentz OJI. Pathophysiology of polytrauma. 2005;36(6):691–709.
78. von Ruden C, Buhren V, Perl M. Polytrauma Management - Treatment of Severely Injured Patients in ER and OR. Zeitschrift Fur Orthopadie Und Unfallchirurgie. 2017;155(5):603-22.
79. Pfeifer R, Heussen N, Michalewicz E, Hilgers RD, Pape HC. Incidence of adult respiratory distress syndrome in trauma patients: A systematic review and meta-analysis over a period of three decades. Journal of Trauma and Acute Care Surgery. 2017;83(3):496-506.
80. Pape HC, Remmers D, Rice J, Ebisch M, Krettek C, Tscherne H. Appraisal of early evaluation of blunt chest trauma: development of a standardized scoring system for initial clinical decision making. J Trauma. 2000;49(3):496-504.
81. Giannoudis PV, Hildebrand F, Pape HC. Inflammatory serum markers in patients with multiple trauma. Journal of Bone and Joint Surgery-British Volume. 2004;86B(3):313-23.
82. Mommsen P, Frink M, Pape HC, van Griensven M, Probst C, Gaulke R, et al. Elevated systemic IL-18 and neopterin levels are associated with posttraumatic complications among patients with multiple injuries: A prospective cohort study. Injury-International Journal of the Care of the Injured. 2009;40(5):528-34.
83. Pfeifer R, Kobbe P, Darwiche SS, Billiar TR, Pape HC. Role of Hemorrhage in the Induction of Systemic Inflammation and Remote Organ Damage: Analysis of Combined Pseudo-Fracture and Hemorrhagic Shock. Journal of Orthopaedic Research. 2011;29(2):270-4.
84. Pfeifer R, Lichte P, Schreiber H, Sellei RM, Schmidt J, Dombroski D, et al. Inhalative vs. systemic IL-10 administration: Differences in the systemic inflammatory response and end-organ inflammation following hemorrhagic shock. Cytokine. 2012;60(1):266-70.
85. Pape HC, Champion HR. Patient assessment in polytrauma: Current trends rely on multiple parameters to improve the prediction of complications and mortality. Injury-International Journal of the Care of the Injured. 2015;46(10):1875-7.
86. Kunitake RC, Howard BM, Kornblith LZ, Christie SA, Conroy AS, Cohen MJ, et al. Individual clotting factor contributions to mortality following trauma. Journal of Trauma and Acute Care Surgery. 2017;82(2):302-8.
87. Pape HC, Lefering R, Butcher N, Peitzman A, Leenen L, Marzi I, et al. The definition of polytrauma revisited: An international consensus process and proposal of the new 'Berlin definition'. J Trauma Acute Care Surg. 2014;77(5):780–6.

88. Fried SJ, Satiani B, Zeeb P. NORMOTHERMIC RAPID VOLUME REPLACEMENT FOR HYPOVOLEMIC SHOCK - AN INVIVO AND INVITRO STUDY UTILIZING A NEW TECHNIQUE. Journal of Trauma-Injury Infection and Critical Care. 1986;26(2):183-8.
89. Regel G, Lobenhoffer P, Grotz M, Pape HC, Lehmann U, Tscherne H. Treatment results of patients with multiple trauma: an analysis of 3406 cases treated between 1972 and 1991 at a German Level I Trauma Center. Journal of Trauma and Acute Care Surgery. 1995;38(1):70–8.
90. Adams DB, Schwab CW. 21-YEAR EXPERIENCE WITH LAND MINE INJURIES. Journal of Trauma-Injury Infection and Critical Care. 1988;28(1):S159-S62.
91. Pepe PE, Dutton RP, Fowler RL. Preoperative resuscitation of the trauma patient. Current Opinion in Anesthesiology. 2008;21(2):216-21.
92. Kreimeier U. Pathophysiology of fluid imbalance. Critical Care. 2000;4:S3-S7.
93. Spahn DR, Schanz U, Pasch T. Criteria for perioperative transfusion. Anaesthesist. 1998;47(12):1011-20.
94. Geeraedts LMG, Kaasjager HAH, van Vugt AB, Frolke JPM. Exsanguination in trauma: A review of diagnostics and treatment options. Injury-International Journal of the Care of the Injured. 2009;40(1):11-20.
95. Giannoudi M, Harwood P. Damage control resuscitation: lessons learned. European Journal of Trauma and Emergency Surgery. 2016;42(3):273-82.
96. Kasotakis G, Sideris A, Yang YC, de Moya M, Alam H, King DR, et al. Aggressive early crystalloid resuscitation adversely affects outcomes in adult blunt trauma patients: An analysis of the Glue Grant database. Journal of Trauma and Acute Care Surgery. 2013;74(5):1215-21.
97. McSwain NE, Champion HR, Fabian TC, Hoyt DB, Wade CE, Eastridge BJ, et al. State of the Art of Fluid Resuscitation 2010: Prehospital and Immediate Transition to the Hospital. Journal of Trauma-Injury Infection and Critical Care. 2011;70(5):S2-S10.
98. Perl VJU, Leroux B, Cook MR, Watson J, Fair K, Martin DT, et al. Damage-control resuscitation and emergency laparotomy: Findings from the PROPPR study. Journal of Trauma and Acute Care Surgery. 2016;80(4):568-74.
99. Tran A, Yates J, Lau A, Lampron J, Matar M. Permissive hypotension versus conventional resuscitation strategies in adult trauma patients with hemorrhagic shock: A systematic review and meta-analysis of randomized controlled trials. Journal of Trauma and Acute Care Surgery. 2018;84(5):802-8.
100. Rezende JB, Rizoli SB, Andrade MV, Ribeiro DD, Lisboa TA, Camargos ER, et al. Permissive Hypotension and Desmopressin Enhance Clot Formation. Journal of Trauma-Injury Infection and Critical Care. 2010;68(1):42-50.
101. Ogura T, Nakamura Y, Nakano M, Izawa Y, Nakamura M, Fujizuka K, et al. Predicting the need for massive transfusion in trauma patients: the Traumatic Bleeding Severity Score. J Trauma Acute Care Surg. 2014;76(5):1243-50.
102. Davis JW, Shackford SR, Mackersie RC, Hoyt DB. BASE DEFICIT AS A GUIDE TO VOLUME RESUSCITATION. Journal of Trauma-Injury Infection and Critical Care. 1988;28(10):1464-7.
103. Kutcher ME, Howard BM, Sperry JL, Hubbard AE, Decker AL, Cuschieri J, et al. Evolving beyond the vicious triad: Differential mediation of traumatic coagulopathy by injury, shock, and resuscitation. Journal of Trauma and Acute Care Surgery. 2015;78(3):516-23.
104. Hess JR, Lindell AL, Stansbury LG, Dutton RP, Scalea TM. The prevalence of abnormal results of conventional coagulation tests on admission to a trauma center. Transfusion. 2009;49(1):34-9.
105. de Biasi AR, Stansbury LG, Dutton RP, Stein DM, Scalea TM, Hess JR. Blood product use in trauma resuscitation: plasma deficit versus plasma ratio as predictors of mortality in trauma. Transfusion. 2011;51(9):1925-32.
106. Stansbury LG, Hess AS, Thompson K, Kramer BM, Scalea TM, Hess JR. The Clinical Significance of Platelet Counts in the First 24 Hours After Severe Injury. Transfusion. 2012;52:32A-A.

107. Floccard B, Rugeri L, Faure A, Saint Denis M, Boyle EM, Peguet O, et al. Early coagulopathy in trauma patients: An on-scene and hospital admission study. Injury-International Journal of the Care of the Injured. 2012;43(1):26-32.
108. Spahn DR, Rossaint R. Coagulopathy and blood component transfusion in trauma. British Journal of Anaesthesia. 2005;95(2):130-9.
109. Spahn DR, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Gordini G, et al. Management of bleeding following major trauma: a European guideline. Critical Care. 2007;11(1):22.
110. Dzik WH, Blajchman MA, Fergusson D, Hameed M, Henry B, Kirkpatrick AW, et al. Clinical review: Canadian National Advisory Committee on Blood and Blood Products - Massive Transfusion Consensus Conference 2011: report of the panel. Critical Care. 2011;15(6):12.
111. Gorlinger K, Kozek-Langenecker SA, Spahn DR. Outcome criteria such as massive transfusion are inadequate for matching and result in questionable conclusions. Journal of Trauma and Acute Care Surgery. 2013;75(4):2.
112. Dzik W. Predicting hemorrhage using preoperative coagulation screening assays. Current hematology reports. 2004;3(5):324-30.
113. Seyve L, Richarme C, Polack B, Marlu R. Impact of four direct oral anticoagulants on rotational thromboelastometry (ROTEM). International Journal of Laboratory Hematology. 2018;40(1):84-93.
114. Bhardwaj V, Malhotra P, Hasija S, Chowdury UK, Pangasa N. Coagulopathies in Cyanotic Cardiac Patients: An Analysis with Three Point-of-care Testing Devices (Thromboelastography, Rotational Thromboelastometry, and Sonoclot Analyzer). Annals of Cardiac Anaesthesia. 2017;20(2):212-8.
115. Biolik G, Kokot M, Sznapka M, Swieszek A, Ziaja D, Pawlicki K, et al. Platelet reactivity in thromboelastometry. Revision of the FIBTEM test: a basic study. Scandinavian Journal of Clinical & Laboratory Investigation. 2017;77(3):216-22.
116. Roszko PJD, Kavanaugh MJ, Boese ML, Longwell JJ, Earley AS. Rotational thromboelastometry (ROTEM) guided treatment of an Afghanistan viper envenomation at a NATO military hospital. Clinical Toxicology. 2017;55(3):229-30.
117. Stein P, Kaserer A, Spahn GH, Spahn DR. Point-of-Care Coagulation Monitoring in Trauma Patients. Seminars in Thrombosis and Hemostasis. 2017;43(4):367-74.
118. Wikkelso A, Wetterslev J, Moller AM, Afshari A. Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding patients: a systematic review with meta-analysis and trial sequential analysis. Anaesthesia. 2017;72(4):519-31.
119. van Wessem KJP, Leenen LPH. Thromboelastography does not provide additional information to guide resuscitation in the severely injured. Anz Journal of Surgery. 2018;88(7-8):697-701.
120. Cotton BA, Faz G, Hatch QM, Radwan ZA, Podbielski J, Wade C, et al. Rapid Thrombelastography Delivers Real-Time Results That Predict Transfusion Within 1 Hour of Admission. Journal of Trauma-Injury Infection and Critical Care. 2011;71(2):407-14.
121. Spahn DR. TEG (R)- or ROTEM (R)-based individualized goal-directed coagulation algorithms: don't wait - act now! Critical Care. 2014;18(6):3.
122. Levi M, Fries D, Gombotz H, van der Linden P, Nascimento B, Callum JL, et al. Prevention and treatment of coagulopathy in patients receiving massive transfusions. Vox Sanguinis. 2011;101(2):154-74.
123. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care. 2016;20:100.
124. Spahn DR, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. Critical Care. 2013;17(2).
125. Holcomb JB, Wade CE, Michalek JE, Chisholm GB, Zarzabal LA, Schreiber MA, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Annals of Surgery. 2008;248(3):447-56.

126. Kashuk JL, Moore EE, Johnson JL, Haenel J, Wilson M, Moore JB, et al. Postinjury life threatening coagulopathy: Is 1 : 1 fresh frozen plasma: Packed red blood cells the answer? Journal of Trauma-Injury Infection and Critical Care. 2008;65(2):261-70.
127. van Wessem KJP, Leenen LPH. Reduction in Mortality Rates of Postinjury Multiple Organ Dysfunction Syndrome: A Shifting Paradigm? A Prospective Population-Based Cohort Study. Shock. 2018;49(1):33-8.
128. Moore EE, Moore HB, Chapman MP, Gonzalez E, Sauaia A. Goal-directed hemostatic resuscitation for trauma induced coagulopathy: Maintaining homeostasis. Journal of Trauma and Acute Care Surgery. 2018;84:S35-S40.
129. Moore HB, Moore EE, Liras IN, Wade C, Huebner BR, Burlew CC, et al. Targeting resuscitation to normalization of coagulating status: Hyper and hypocoagulability after severe injury are both associated with increased mortality. American Journal of Surgery. 2017;214(6):1041-5.
130. Moore HB, Moore EE, Chapman MP, Hansen KC, Cohen MJ, Pieracci FM, et al. Does Tranexamic Acid Improve Clot Strength in Severely Injured Patients Who Have Elevated Fibrin Degradation Products and Low Fibrinolytic Activity, Measured by Thrombelastography? J Am Coll Surg. 2019;229(1):92-101.
131. Batibay SG, Turkmen I, Duman S, Camur S, Saglam N, Batibay S. Is tranexamic acid safe and reliable during tibial intramedullary nailing? Ulusal Travma Ve Acil Cerrahi Dergisi-Turkish Journal of Trauma & Emergency Surgery. 2018;24(6):575-80.
132. Schiavone A, Bisaccia M, Inkov I, Rinonapoli G, Manni M, Rollo G, et al. Tranexamic Acid in Pertrochanteric Femoral Fracture: Is it a Safe Drug or Not? Folia Med (Plovdiv). 2018;60(1):67-78.
133. Goldstein M, Feldmann C, Wulf H, Wiesmann T. Tranexamic Acid Prophylaxis in Hip and Knee Joint Replacement. Deutsches Arzteblatt International. 2017;114(48):824-+.
134. Huebner BR, Dorlac WC, Cribari C. Tranexamic Acid Use in Prehospital Uncontrolled Hemorrhage. Wilderness & Environmental Medicine. 2017;28(2):S50-S60.
135. Ramirez RJ, Spinella PC, Bochicchio GV. Tranexamic Acid Update in Trauma. Critical Care Clinics. 2017;33(1):85-+.
136. Huckabee WE. ABNORMAL RESTING BLOOD LACTATE .1. SIGNIFICANCE OF HYPERLACTATEMIA IN HOSPITALIZED PATIENTS. American Journal of Medicine. 1961;30(6):833-&.
137. Huckabee WE. ABNORMAL RESTING BLOOD LACTATE .2. LACTIC ACIDOSIS. American Journal of Medicine. 1961;30(6):840-&.
138. Weil MH, Michaels S, Rackow EC. COMPARISON OF BLOOD LACTATE CONCENTRATIONS IN CENTRAL VENOUS, PULMONARY-ARTERY, AND ARTERIAL BLOOD. Critical Care Medicine. 1987;15(5):489-90.
139. Aukema TS, Hietbrink F, Beenen LFM, Leenen LPH. Does thoracic injury impair the predictive value of base deficit in trauma patients? Injury-International Journal of the Care of the Injured. 2010;41(9):935-7.
140. Dunham MP, Sartorius B, Laing GL, Bruce JL, Clarke DL. A comparison of base deficit and vital signs in the early assessment of patients with penetrating trauma in a high burden setting. Injury. 2017;48(9):1972-7.
141. Guyette F, Suffoletto B, Castillo JL, Quintero J, Callaway C, Puyana JC. Prehospital Serum Lactate as a Predictor of Outcomes in Trauma Patients: A Retrospective Observational Study. Journal of Trauma-Injury Infection and Critical Care. 2011;70(4):782-6.
142. Dübendorfer C, Billeter AT, Seifert B, Keel M, Turina M. Serial lactate and admission SOFA scores in trauma: an analysis of predictive value in 724 patients with and without traumatic brain injury. Eur J Trauma Emerg Surg. 2013;39(1):25-34.
143. Regnier MA, Raux M, Le Manach Y, Asencio Y, Gaillard J, Devilliers C, et al. Prognostic Significance of Blood Lactate and Lactate Clearance in Trauma Patients. Anesthesiology. 2012;117(6):1276-88.

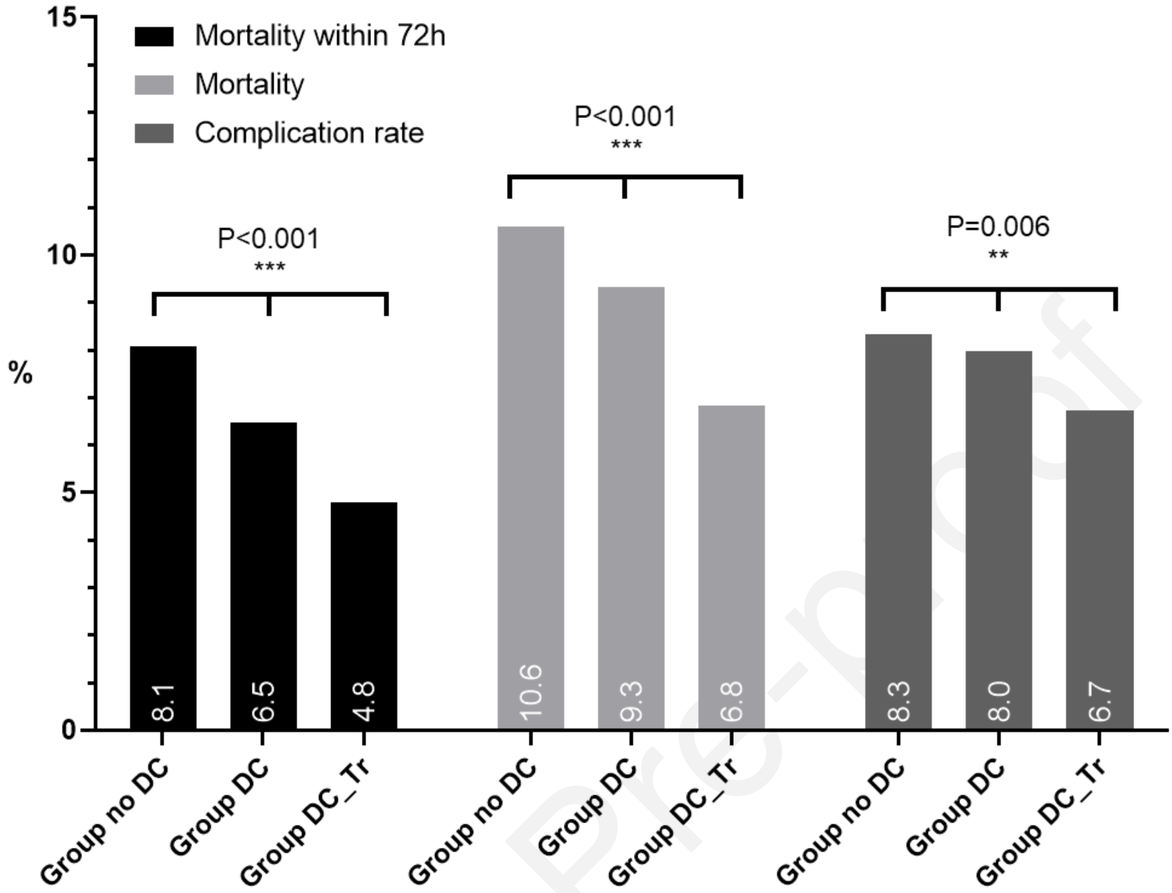
144. Billeter A, Turina M, Seifert B, Mica L, Stocker R, Keel M. Early serum procalcitonin, interleukin-6, and 24-hour lactate clearance: useful indicators of septic infections in severely traumatized patients. World journal of surgery. 2009;33(3):558-66.
145. Abramson D, Scalea TM, Hitchcock R, Trooskin SZ, Henry SM, Greenspan J. Lactate clearance and survival following injury. The Journal of trauma. 1993;35(4):584-8; discussion 8-9.
146. Gallagher EJ, Rodriguez K, Touger M. Agreement between peripheral venous and arterial lactate levels. Ann Emerg Med. 1997;29(4):479-83.
147. van Tienhoven AJ, van Beers CAJ, Siegert CEH. Agreement between arterial and peripheral venous lactate levels in the ED: A systematic review. Am J Emerg Med. 2019;37(4):746-50.
148. Dezman ZDW, Corner AC, Smith GS, Hu PF, Mackenzie CF, Scalea TM, et al. Repeat lactate level predicts mortality better than rate of clearance. American Journal of Emergency Medicine. 2018;36(11):2005-9.
149. Vallier HA, Cureton BA, Ekstein C, Oldenburg FP, Wilber JH. Early definitive stabilization of unstable pelvis and acetabulum fractures reduces morbidity. J Trauma. 2010;69(3):677-84.
150. Dezman ZDW, Comer AC, Narayan M, Scalea TM, Hirshon JM, Smith GS. Alcohol consumption decreases lactate clearance in acutely injured patients. Injury-International Journal of the Care of the Injured. 2016;47(9):1908-12.
151. Stang M, Wysowski DK, Butler-Jones D. Incidence of lactic acidosis in metformin users. Diabetes Care. 1999;22(6):925-7.
152. Lange CM, Bojunga J, Hofmann WP, Wunder K, Mihm U, Zeuzem S, et al. Severe Lactic Acidosis During Treatment of Chronic Hepatitis B with Entecavir in Patients with Impaired Liver Function. Hepatology. 2009;50(6):2001-6.
153. Almenoff PL, Leavy J, Weil MH, Goldberg NB, Vega D, Rackow EC. Prolongation of the half-life of lactate after maximal exercise in patients with hepatic dysfunction. Crit Care Med. 1989;17(9):870-3.
154. Guzzo JL, Bochicchio GV, Napolitano LM, Malone DL, Meyer W, Scalea TM. Prediction of outcomes in trauma: Anatomic or physiologic parameters? Journal of the American College of Surgeons. 2005;201(6):891-7.
155. Hildebrand F, Lefering R, Andruszkow H, Zelle BA, Barkatali BM, Pape HC. Development of a scoring system based on conventional parameters to assess polytrauma patients: PolyTrauma Grading Score (PTGS). Injury. 2015;46 Suppl 4:S93-8.
156. Shackelford S, Yang S, Hu P, Miller C, Anazodo A, Galvagno S, et al. Predicting blood transfusion using automated analysis of pulse oximetry signals and laboratory values. J Trauma Acute Care Surg. 2015;79(4 Suppl 2):S175-80.
157. Mackenzie CF, Wang Y, Hu PF, Chen SY, Chen HH, Hagegeorge G, et al. Automated prediction of early blood transfusion and mortality in trauma patients. J Trauma Acute Care Surg. 2014;76(6):1379-85.
158. Murthi SB, Fatima S, Menne AR, Glaser JJ, Galvagno SM, Biederman S, et al. Ultrasound assessment of volume responsiveness in critically ill surgical patients: Two measurements are better than one. J Trauma Acute Care Surg. 2017;82(3):505-11.
159. Dienstknecht T, Rixen D, Giannoudis P, Pape HC, Grp ES. Do Parameters Used to Clear Noncritically Injured Polytrauma Patients for Extremity Surgery Predict Complications? Clinical Orthopaedics and Related Research. 2013;471(9):2878-84.
160. Nahm NJ, Moore TA, Vallier HA. Use of two grading systems in determining risks associated with timing of fracture fixation. J Trauma Acute Care Surg. 2014;77(2):268-79.
161. Pape H, Andruszkow H, Pfeifer R, Hildebrand F, Barkatali B. Options and hazards of the early appropriate care protocol for trauma patients with major fractures: towards safe definitive surgery. Injury. 2016;47(4):787-91.
162. Schreiber VM, Tarkin IS, Hildebrand F, Darwiche S, Pfeifer R, Chelly J, et al. The timing of definitive fixation for major fractures in polytrauma-A matched-pair comparison between a US and

European level I centres: Analysis of current fracture management practice in polytrauma. Injury-International Journal of the Care of the Injured. 2011;42(7):650-4.
163. Steinhausen E, Lefering R, Tjardes T, Neugebauer EA, Bouillon B, Rixen D, et al. A risk-adapted approach is beneficial in the management of bilateral femoral shaft fractures in multiple trauma patients: an analysis based on the trauma registry of the German Trauma Society. J Trauma Acute Care Surg. 2014;76(5):1288-93.
164. Brundage SI, McGhan R, Jurkovich GJ, Mack CD, Maier RV. Timing of femur fracture fixation: Effect on outcome in patients with thoracic and head injuries. Journal of Trauma-Injury Infection and Critical Care. 2002;52(2):299-307.
165. Bone LB, Johnson KD, Weigelt J, Scheinberg R. Early versus delayed stabilization of femoral fractures. A prospective randomized study. J Bone Joint Surg Am. 1989;71(3):336-40.
166. Loftis KL, Price J, Gillich PJ. Evolution of the Abbreviated Injury Scale: 1990-2015. Traffic Inj Prev. 2018;19(sup2):S109-S13.
167. Palmer CS, Gabbe BJ, Cameron PA. Defining major trauma using the 2008 Abbreviated Injury Scale. Injury. 2016;47(1):109-15.
168. Scalea TM, Boswell SA, Scott JD, Mitchell KA, Kramer ME, Pollack AN. External fixation as a bridge to intramedullary nailing for patients with multiple injuries and with femur fractures: Damage control orthopedics. Journal of Trauma-Injury Infection and Critical Care. 2000;48(4):613-21.
169. Kobbe P, Micansky F, Lichte P, Sellei RM, Pfeifer R, Dombroski D, et al. Increased morbidity and mortality after bilateral femoral shaft fractures: Myth or reality in the era of damage control? Injury-International Journal of the Care of the Injured. 2013;44(2):221-5.
170. Pape HC. Damage-Control Orthopaedic Surgery in Polytrauma: Influence on the Clinical Course and Its Pathogenetic Background. In: Bentley G, editor. European Instructional Lectures, Vol 9, 2009. European Instructional Course Lectures. 9. Dordrecht: Springer; 2009. p. 67-74.
171. Pape HC, Hildebrand F, Krettek C. Decisions and priorities of operative treatment during shock room treatment. Unfallchirurg. 2004;107(10):927-+.
172. Kobbe P, Tarkin IS, Oberbeck R, Pape HC. Damage Control Orthopaedics in Polytraumatised Patients with Lower Leg Injuries. Zeitschrift Fur Orthopadie Und Unfallchirurgie. 2008;146(5):580-5.
173. Hildebrand F, Giannoudis P, Krettek C, Pape HC. Damage control: extremities. Injury-International Journal of the Care of the Injured. 2004;35(7):678-89.
174. Guerado E, Bertrand ML, Cano JR, Cervan AM, Galan A. Damage control orthopaedics: State of the art. World Journal of Orthopedics. 2019;10(1):1-13.
175. Giannoudis PV, Giannoudi M, Stavlas P. Damage control orthopaedics: lessons learned. Injury. 2009;40 Suppl 4:S47-52.
176. Rigal S, Mathieu L, de l'Escalopier N. Temporary fixation of limbs and pelvis. Orthopaedics & Traumatology-Surgery & Research. 2018;104(1):S81-S8.
177. Blokhuis TJ, Pape HC, Frolke JP. Timing of definitive fixation of major long bone fractures: Can fat embolism syndrome be prevented? Injury-International Journal of the Care of the Injured. 2017;48:S3-S6.
178. Choufani C, Barbier O, Grosset A, Murison JC, Ollat D, Rigal S, et al. Initial management of complex hand injuries in military or austere environments: how to defer and prepare for definitive repair? International Orthopaedics. 2017;41(9):1771-5.
179. Gasser B, Tiefenboeck TM, Boesmueller S, Kivaranovic D, Bukaty A, Platzer P. Damage control surgery - experiences from a level I trauma center. Bmc Musculoskeletal Disorders. 2017;18:7.
180. Dong CH, Wang ZM, Zhao XL, Wang AM. The use of damage control orthopaedics to minimize negative sequelae of surgery delay in elderly comorbid patients with hip fracture. European Review for Medical and Pharmacological Sciences. 2016;20(12):2505-14.
181. Ng C, Mifsud M, Borg JN, Mizzi C. The Libyan civil conflict: selected case series of orthopaedic trauma managed in Malta in 2014. Scandinavian Journal of Trauma Resuscitation & Emergency Medicine. 2015;23:10.

182. Pape HC, Pfeifer R. Safe definitive orthopaedic surgery (SDS): Repeated assessment for tapered application of Early Definitive Care and Damage Control? An inclusive view of recent advances in polytrauma management. Injury-International Journal of the Care of the Injured. 2015;46(1):1-3.
183. Pape HC, Andruszkow H, Pfeifer R, Hildebrand F, Barkatali BM. Options and hazards of the early appropriate care protocol for trauma patients with major fractures: Towards safe definitive surgery. Injury-International Journal of the Care of the Injured. 2016;47(4):787-91.
184. Giannoudis PV, Giannoudis VP, Horwitz DS. Time to think outside the box: 'Prompt-Individualised-Safe Management' (PRISM) should prevail in patients with multiple injuries. Injury-International Journal of the Care of the Injured. 2017;48(7):1279-82.
185. Mommsen P, Zeckey C, Andruszkow H, Weidemann J, Fromke C, Puljic P, et al. Comparison of different thoracic trauma scoring systems in regards to prediction of post-traumatic complications and outcome in blunt chest trauma. J Surg Res. 2012;176(1):239–47.
186. Haider T, Halat G, Heinz T, Hajdu S, Negrin LL. Thoracic trauma and acute respiratory distress syndrome in polytraumatized patients: a retrospective analysis. Minerva Anestesiologica. 2017;83(10):1026-33.
187. Bayer J, Lefering R, Reinhardt S, Kuhle J, Zwingmann J, Sudkamp NP, et al. Thoracic trauma severity contributes to differences in intensive care therapy and mortality of severely injured patients: analysis based on the TraumaRegister DGU (R). World Journal of Emergency Surgery. 2017;12:9.
188. Daurat A, Millet I, Roustan JP, Maury C, Taourel P, Jaber S, et al. Thoracic Trauma Severity score on admission allows to determine the risk of delayed ARDS in trauma patients with pulmonary contusion. Injury. 2016;47(1):147–53.
189. Sormann P, Lustenberger T, Relja B, Marzi I, Wutzler S. Role of biomarkers in acute traumatic lung injury. Injury-International Journal of the Care of the Injured. 2017;48(11):2400-6.
190. Hughes KT, Beasley MB. Pulmonary Manifestations of Acute Lung Injury More Than Just Diffuse Alveolar Damage. Archives of Pathology & Laboratory Medicine. 2017;141(7):916-22.
191. Kornblith LZ, Howard BM, Cheung CK, Dayter Y, Pandey S, Busch MP, et al. The whole is greater than the sum of its parts: Hemostatic profiles of whole blood variants. Journal of Trauma and Acute Care Surgery. 2014;77(6):818-27.
192. Kornblith LZ, Robles AJ, Conroy AS, Redick BJ, Howard BM, Hendrickson CM, et al. PREDICTORS OF POST-INJURY ARDS: LUNG INJURY PERSISTS IN THE ERA OF HEMOSTATIC RESUSCITATION. J Trauma Acute Care Surg. 2019.
193. Rotondo MF, Zonies DH. The damage control sequence and underlying logic. Surgical Clinics of North America. 1997;77(4):761-&.
194. Pape HC, Stalp M, von Griensven M, Weinberg A, Dahlweit M, Tscherne H. Optimal timing for secondary surgery in polytrauma patients: an evaluation of 4314 serious-injury cases. Chirurg. 1999;70(11):1287-93.
195. Dienstknecht T, Rixen D, Giannoudis P, Pape H-C, Group ES. Do parameters used to clear noncritically injured polytrauma patients for extremity surgery predict complications? Clinical Orthopaedics and Related Research®. 2013;471(9):2878-84.
196. Enninghorst N, Peralta R, Yoshino O, Pfeifer R, Pape HC, Hardy BM, et al. Physiological assessment of the polytrauma patient: initial and secondary surgeries. Eur J Trauma Emerg Surg. 2011;37(6):559-66.

LEGENDS

FIGURE 1 Results regarding complications between 3 groups: DC; No DC and DC Tr



DC: Damage control; **No DC:** No Damage control; **DC Tr:** Damage control and application of new transfusion guidelines

TABLE 1 Changes in resuscitation strategies

Author	Year	Patient Number	Origin	Main finding
Gonzalez	2007	200	Level 1 Center	FFP should be administered during resuscitation, not just volume
Duchesne	2010	124	Level 1 Center	DCR and DCL improve survival and reduce ICU stay
Cotton	2011	390	Level 1 Center	Damage Control Resuscitation improves 30 days survival
Holcomb	2015	680	PROPPR Study	1:1:1 plasma:platelet:pRBCS improves 24 hours exsanguination
Perl	2016	346	PROPPR Study	No side effect by permissive resuscitation on emergency laparotomy
Meyer	680	680	PROPPR Study	Critical administration threshold should be respected
Robinson	454	454	PROPPR Study	Excess crystalloids increase the risk of ARDS

FFP = Fresh Frozen Plasma

DCR = Damage Control Resuscitation

DCL = Damage Control Laparotomy

pRBCs = packed Red Blood Cells

ARD = Acute Respiratory Distress Syndrome

TABLE 2 Summary of coagulation tests recommended in guidelines, multi center studies and systematic reviews. Also, threshold levels for dynamic platelet function tests regarding prediction of various complications are listed, along with comparative parameters indicated in the studies

Author	year	Patients	Endpoint Parameter	Comparative parameter
Guidelines/Reviews				
Rugieri	**2007**	**General trauma**	**INTEM CA15**	**Platelet count**
Holcomb	**2012**	**ER patients**	**r-TEG (non-specific)**	**CCTs**
Veigas	**2016**	**Systematic review**	**EXTEM/INTEM**	**multiple CCTs**
Spahn	**2019**	**Guideline**	**all**	**multiple CCTs**
Schochl	**2019**	**Multicenter**	**all**	**multiple CCTs**
Prediction of Mortality				
Levrat	**2008**	**General trauma**	**EXTEM MCF/APTEM**	**ELT<90min**
Schochl	**2009**	**General trauma**	**FIBTEM MCF/EXTEM**	**none**
Tauber	**2011**	**see above**	**FIBTEM/EXTEM**	**CCT**
Rourke	**2012**	**General trauma**	**EXTEM/FIBTEM**	**none**
Prediction of mass transfusion				
Leemann	**2010**	**General trauma**	**EXTEM/INTEM**	**CCT**
Tauber	**2011**	**Polytrauma**	**FIBTEM MCF**	**CCT**
Schochl	**2011**	**Head injury**	**FIBTEM**	**CCT**
Davenport	**2011**	**General trauma**	**EXTEM**	**CCT**
All transfusions				
Hagemo	**2015**	**General trauma**	**EXTEM/FIBTEM**	**CCT**
Schochl	**2010**	**Major Trauma**	**EXTEM/FIBTEM**	**CCT**

CCT = Conventional Coagulatory tests

ELT = Euglobulin Lysis Time

TABLE 3 Recommended lactate threshold levels and availability of lactate clearance data – all trauma patients

Author	Year	Lactate Threshold (admission)	Lactate Clearance (24 hours)	Other comparative values	
Husain	2003	2.0 mmol/l	arterial	2.0 mmol/l	BD, Apache II
Pape	2005	2.5 mmol/l	n.a.	n.a.	> 6
Billeter	2009	2.5 mmol/l	arterial	2.5mmol/l	PCT, Il-6
Regnier	2012	2.0 mmol/l	n.a.	2.2mmol/l at 2,4 hours	RTS, TRISS
Odom	2013	2.5 mg/dl	n.a.	2.5 mmol/l at 6 hours	n.a.
Vallier	2014	4.0 mmol/l	n.a.	n.a.	pH 7.25
Dezman	2015	3.0 mmol/l	venous	2.0 mmol/l	Age, ISS, adm. BP
Contenti	2015	2.2 mmol/l	mismatch	n.a.	none
Dekker	2017	2.5 mmol/l	no difference	2.5 mmol/l	ISS, TRISS
Dezman	2018	3.0 mmol/l	venous	2.0 mmol/l	n.a.
Thienhoven	2019	2.0 mmol/l	arterial	n.a.	n.a.

BD = Base Deficit

n.a. = not available

PCT = Procalcitonine

IL = Interleukine

RTS = revised Trauma Score

TRISS = Trauma Injury Severity Score

ISS = Injury Severity Score

Adm. = admission

BP = Blood Pressure

TABLE 4 Comparison of parameters to perform various scores performed for grading of polytrauma patients in the orthopaedic literature

Categories		Score			
		CGS	EAC	mCGS	PTGS
		2005	2013	2014	2014
Shock					
	SBP, mmHg	x		x	x
	PBRC	(2 hrs)		(24 hrs)	(48 hrs)
	Lactate, mmol/L	x	x	x	
	BE, mEq/L	x	x	x	x
	pH		x		
	ATLS score	x			
	Urine output	x			
Coagulopathy					
	Platelet count	x		x	
	Factor II/V	x			
	Fibrinogen	x			
	D-Dimer	x			
	INR < 2				x
Admission Temperature		x		x	
Soft Tissue Injury					
	PaO_2/FiO_2	x			
	AIS chest	x		x	
	Thoracic Trauma Score	x			
	Moore OIS	x		x	
	Extremity AIS	x		x	
	Pelvic trauma AO	x			
Injury Severity					
	NISS				x

(m)CGS = (modified) Clinical Grading Score
EAC = Early Appropriate Care
PTGS = PolyTrauma Grading Score
SBP = Systolic Blood Pressure
PBRC = Packed Red Blood Cells
BE = Base Excess
ATLS = Advanced Trauma Life Support
INR = International Normalized Ratio
AIS = Abbreviated Injury Scale
OIS = Organ Injury Score

AO = Arbeitsgemeinschaft für Osteosynthesefragen
NISS = New Injury Severity Score

TABLE 5 Injury severity level in clinical studies and comparison of indications for early definitive techniques and damage control orthopedics

Author	Year	Setting	DC use	Mean ISS surgery <24h Early definitive surgery	Mean ISS surgery >24h Damage control	Conclusion
Nowotarsky	2000	single center	n.a. (112/1507, all femurs)	n.a.	n.a.	DC is safe in selected patients
Brundage	2002	single center	n.a. 157/674 nonoperative	-	-	Early operation is beneficial
Taeger	2005	single center	30.70%	30.4	37.3	TRISS 20 vs 39%29.5 vs 24.3% TRISS
Pape	2007	10 centers (RCT)	n.a.	23.3	29	Early fixation in stable, DCO in unstable
Morshed	2009	Registry (NTDB)	n.a.	27.2	32.3	Less mortality in DCO with abd. trauma
Tuttle	2009	single center	8.40%	n.a.	n.a.	DCO is safe
O'Toole	2009	single center	n.a.	27.4	36.2	DCO rarer than in Europe
Lefaivre	2010	2 centers	21.4% and 2.77%	n.a.	n.a.	No difference
Nahm	2011	single center	n.a.	28.8	36.4	Early definitive care

Vallier	2013	single center	n.a.	exFix in late group	n.a.	Early definitive care
Steinhausen	2014	Registry (TR-DGU)	n.a.	23.5	31.1	"Risk –adapted ", if in doubt: DCO
Pape	2019	single center	27.1%	26.5	30.3	risk adapted DCO in unstable patients

DC = Damage Control

TRISS = Trauma Injury Severity Score

DCO = Damage Control Orthopaedic

n.a. = Not available

RCT = Randomized Controlled Trial

NTDB = National Trauma Data Base

TR-DGU = Trauma Register Deutsche Gesellschaft für Unfallchirurgie (German Society for Trauma Surgery)

h = hours

TABLE 6 Demographics of included patients from a database (level 1 trauma center)

n	**3668**
Age, mean (SD)	**45.8 (20.1)**
Sex, male n (%)	**2694 (73.4)**
Mortality within 72h, n (%)	**709 (19.4)**
Emergency Surgery at admission, n (%)	**2592 (74.4)**
Duration of emergency surgery, mean (SD)	**111.4 (96.6)**
Length of Stay, mean (SD)	**16.9 (18.7)**
ICU Stay, mean (SD)	**8.2 (10.5)**
Duration Ventilation, mean (SD)	**5.1 (8.1)**
AIS Head, mean (SD)	**2.8 (1.9)**
AIS Face, mean (SD)	**0.6 (1.0)**
AIS Thoracic, mean (SD)	**1.6 (1.7)**
AIS abdomen, mean (SD)	**1.0 (1.7)**
AIS spine, mean (SD)	**0.8 (1.4)**
AIS pelvis, mean (SD)	**0.6 (1.2)**
AIS extremity, mean (SD)	**1.3 (1.4)**
ISS, mean (SD)	**28.2 (15.1)**

NISS, mean (SD)	**37.1 (17.4)**
GCS admission, mean (SD)	**8.8 (5.5)**
Lactate admission, mean (SD)	**2.9 (2.5)**
Hemoglobin admission, mean (SD)	**11.4 (4.0)**
ROTEM Intem CT admittion, n (%)	**193 (5.3)**
Mortality, n (%)	**982 (26.8)**
Pneumonia, n (%)	**623 (19.1)**
Sepsis, n (%)	**546 (15.0)**
Septic shock, n(%)	**119 (3.3)**
Bacteremia, n(%)	**254 (7.9)**

n = Number

SD = Standard Deviation

h = Hours

ICU = Intensive Care Unit

AIS = Abbreviated Injury Scale

(N)ISS = (New) Injury Severity Score

GCS = Glasgow Coma Scale

TABLE 7 Variability of lactate threshold levels and recommendations of surgical timing in the orthopaedic literature.

Author	Journal	year	Patient Number	Inclusion period	Time of surgery	Lactate threshold
O'Toole Probst	J. Trauma-Injury Infect. Crit. Care	2009	582	2002-2005	24 hours	2.5mmol/l
Vallier	J. Orthop. Trauma	2013	1443	1999-2006	24 hours	4 mmol/l
Nahm	J. Trauma Acute Care Surg	2014	1443	n.a.	24 hours	4 mmol/l
Vallier	J. Orthop. Surg. Res	2015	335	30 months	36 hours	4 mmol/l
Weinberg	J. Orthop. Surg. Res	2015	332	2010-2013	36 hours	4 mmol/l
Vallier	J. Orthop. Trauma	2016	253	18 months	36 hours	n.a.
Childs	J. Orthop. Trauma	2017	376	30 months	24 hours	2 mmol/l

TABLE 8 Comparison of published treatment guidelines and protocols

	ETC	**DC**	***EAC***	***SDS***	***PRISM***
Year of Introduction	1989	2000	2013	2015	2016
Supportive Prosp. Randomized study	Yes (Ref 165) 1989	Yes (Ref 12) 2007	No	No	No
Supportive Registry analysis	No	Yes (Ref 163) 2014	No	No	No
Matched pair analysis	No	Yes (Ref 162) 2011	No	No	No

Table 9 Parameters to assess the patient at risk, comparison between 2000 and currently.

Parameters to assess the borderline trauma patient - comparison between 2000 and now

		2000	**2020** *unchanged parameters* **new parameters**
Static parameters	*Injury combination*	*Polytrauma ISS > 20 and* *additional thoracic trauma (AIS >2)*	*Polytrauma ISS > 20 and AIS chest > 2* **Thoracic Trauma Score (TTS) > grade 2** **(> 3 rib fx, paO_2/FiO_2 <200, LuCo > 1 lobe, bilat.HT/HPT > unilat)**
	Local injury chest	*Bilateral lung contusion:* *1st plain film*	*Bilateral lung contusion: 1st plain film or* **Chest CT:** • **unilateral bisegmental contusion** • **bilateral uni- or bisegmental contusion** • **flail chest**

	Local injury trunk/extremities	*Multiple long bone fractures + truncal injury AIS 2 or more*	*Multiple long bone fractures + truncal injury AIS 2 or more*
	Truncal /	*Polytrauma with abdominal /pelvic trauma RR ,90 mm Hg) (Moore 3) and hem. shock*	*Polytrauma with abdominal/pelvic trauma RR ,90 mm Hg) (Moore 3) and hemorrhagic shock*
	Major Surgery for *non-life saving conditions*	*Day 1 surgery* *(Early total care)* *or wait until 4-6* *(window of opportunity)*	**Non life saving surgeries** **Flexible (day 1, 2, 3) after reassessment according to individual patient physiology:** **Safe definitive surgery (SDS) and damage control (DCO)**
	Duration of 1st operative intervention	*Presumed operation time > 6 hours*	*Presumed operation time > 6 hours* **intraoperative reassessment:** • **coagulopathy (ROTEM/FIBTEM)** • **lactate (< 2.0 - 2.5 mmol/L)** • **body temperature stable** • **requirement > 3 pRBC / hour**
Dynamic		*Massive transfusion* (10 units RBCs per 24 hours)	

parameters	*Blood transfusion requirements*		***Massive transfusion*** **(10 units RBCs per 6 hours)** **initiates „goal directed therapy" (massive transfusion protocols)**
	Intra/ perioperative	*PA-pressure increase during intramedullary nailing .6 mm Hg* *Initial mean PAP<24 mm Hg*	• **ROTEM/FIBTEM** • **Lactate clearance < 2.5 mmol/l (24 hrs.)**

LuCo = Lung contusion