# FROM CRISIS TO CONTROL - UNDERSTANDING THE CONCEPT DAMAGE CONTROL RESUSCITATION

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**UNIVERSITY OF RIJEKA**
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Thesis mentor: Prof. Željko Župan, MD, PhD

The graduation thesis was graded on 29.02.2024 in Rijeka, before the Committee composed of the following members:

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3. Prof. Igor Medved, MD, PhD

The graduation thesis contains 28 pages, 2 figures, 0 tables, 31 references.

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# 1. LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| AAT | Abdominal Aortic Tourniquet |
| APPT | activated partial thromboplastin time |
| BP | blood pressure |
| CPR | Cardiopulmonary Resuscitation |
| DC | damage control |
| DCR | damage control resuscitation |
| DCS | damage control surgery |
| ER | emergency room |
| FFP | fresh frozen plasma |
| FVII | factor VII |
| FXIII | factor XIII |
| GCS | Glasgow Coma Scale |
| HR | heart rate |
| ICU | Intensive Care Unit |
| IPC | intermittent pneumatic compression |
| ISS | Injury Severity Score |
| iv. | intravenously |
| INR | international normalized ratio |
| MTP | Massive Transfusion Protocol |
| PCC | prothrombin complex concentrate |
| PP | pulse pressure |
| pRBC | packed red blood cells |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| REBOA | Resuscitative Endovascular Balloon Occlusion of the Aorta |
| ROTEM | rotational thromboelastometry |
| RR | respiratory rate |
| RTS | Revised Trauma Score |
| TBI | traumatic brain injury |
| TEG | thromboelastography |
| TF | tissue factor |
| TIVS | Temporary Intravascular Shunt |

| | |
|---|---|
| TRISS | Trauma and Injury Severity Score |
| TXA | tranexamic acid |

## 2. INTRODUCTION

Head and brain injury are leading causes for disability and death in young population (1). Acute traumatic coagulopathy due to bleeding and hemorrhagic shock is responsible for a major part of deaths in patients with multiple and severe trauma. Appropriate and timely initial resuscitation is therefore of special importance in the process of adequate management of the severely injured trauma patients.

The term damage control (DC) was firstly implemented in the beginning of 17$^{th}$ century. The British Royal Navy used this phrase to describe immediate actions the crew of a ship had to perform in case the integrity of a ship's shell had been compromised. These provisional sanctions prevented the ship from sinking and served the sole purpose of enabling its safe return to the nearest port for definite repairs (2).

Trying to cope with severe blood loss, acidosis and hypothermia in order to preserve life in trauma patients, the concept of DC was analogously implemented in modern medicine at the end of the 1970s under the term damage control surgery (DCS) (3). This new strategic approach was firstly used in patients with penetrating injuries of the abdomen associated with massive bleeding and quickly gained popularity especially in military medicine. It introduced the methodology for stabilizing the trauma patients, minimalizing blood loss until definitive hemostasis and correction of ongoing metabolic derangements by early initiating surgery. The goals were to control hemorrhage, decontaminate the abdominal cavity and to pack and rapidly close the abdomen instead of doing definitive and reconstructive laparotomy in the first place (2). These temporary measures served to stabilize the patient for transport from the battlefield to definitive treatment facility. The concept of DCS soon was established in civilian settings, too. In fact, it laid the foundation for a multistep approach to deal with heavily injured patients and the concept of damage control resuscitation (DCR) was born.

DCR nowadays is used in various medical disciplines. Its treatment algorithm composes of different stages optimized to deal with severe hemorrhage, to correct or prevent the lethal triad of trauma composed of hypothermia, acidosis, and coagulopathy, and to increase the overall chance for survival for the patient.

The first step aims to achieve hemostasis, decontaminate the wound, and close it temporarily.

In a second step, physiologic abnormalities of the trauma patient are corrected. This usually happens at an ICU.

Finally, when the patient is stable, the definitive surgical management is performed (4).

The concept of DCR differs significantly from traditional approach of dealing with heavily injured patients. Before implementation of DCR, the treatment of severe blood loss traditionally focused on aggressive fluid resuscitation with crystalloids to maintain a close to normal and stable blood pressure. Nowadays it is known that excessive crystalloid fluid administration might induce and promote coagulopathy and with the term permissive hypotension even the tolerance for significantly lower blood pressures in trauma patients than physiologically normal is promoted. Furthermore, traditionally trauma patients received definite surgical treatment as e.g. time-consuming complicated reconstruction surgeries despite being in critical condition. Even, when having survived these long and strenuous procedures, derailment in patient's physiological state afterwards would often lead to late mortality due to multiple organ failure. (4) This management strategy changed dramatically, as nowadays in initial stage of treatment in patients in a critical condition the gold standard is to only perform surgery to achieve hemodynamical stability. Further procedures are postponed until the patient's general condition allows it.

## 3. AIMS AND OBJECTIVES

Even though the concept of DCR is not a new one anymore, it is still not commonly known and therefore not used by many physicians, escorting severely injured patients from site of accident to the hospitals, or working at the ER, ICU, and operating theaters.
Therefore, this paper aims to explain the pathomechanisms connected with severe hemorrhage in trauma as well as to summarize proper initial treatment options to ensure optimal care and the best possible outcome for heavily injured patients.

## 4. PATHOPHYSIOLOGY

Bleeding traditionally can be classified into four stages based on percental amount of blood loss of normal blood volume.
In Stage 1 the lost blood is less than 15%. The absolute number depends on the patient but can be estimated as up to 750ml. The patient's organism usually has no problem with compensating for that on its own. The heart rate (HR) might be slightly increased. Blood pressure (BP) as well as pulse pressure (PP) and respiratory rate (RR) are typically unchanged.
In Stage 2 the blood loss is between 15% and 30%, which equals a total of approximately 750 to 1500ml. Vital signs are changed with expected values for HR 100-120 bpm, RR 20-24 and narrow PP. Systolic BP remains at normal levels or might be slightly decreased.

Stage 3 is characterized by blood loss between 30% and 40% or 1500-2000ml. BP drops significantly, HR is greater than 120 and RR is significantly increased as well. Additionally, urine output decreases and capillary refill time is prolonged. Changes in the patient's mental status can be observed.

In Stage 4 the blood loss is higher than 40%. In comparison to Stage 3 Hypotension is even more pronounced and HR is further increased. Urine output might be minimal or absent. The patient's mental status is progressively worse.

The afore mentioned values refer to a 70kg, male patient with a total blood volume of approximately 7% of body weight or in total round about 5 liters. It has to be kept in mind that these values change with patient's biological sex, age and weight (5).

Special attention has to be paid to several groups of patients. In athletes, HR under normal conditions might well be under 50 bpm. Here, in case of hemorrhage, a relative tachycardia can be considered as significant already under 100 bpm. In elderly patients the organism's ability to cope for blood loss might be decreased. In this case, BP will drop already in minor bleedings. Another special case are pregnant women. They physiologically have and increased circulating blood volume, increased HR and RR which makes determination of amount of blood loss harder. Special attention is also indicated in patients under the influence of beta-blockers. Blood loss will not result in compensatory increase in HR which leads to a high risk of underestimating the severity of the patient's condition. Additionally, the incapability to increase HR might lead to an easier drop in BP. The same applies to patients with an artificial pacemaker.

To gain a deeper understanding about the challenges, health care workers must face, when dealing with severely injured patients, it is of importance to understand the different pathophysiological processes that life threatening trauma will induce in any individual patient. Targeting and correcting each one of them leads the path to successful resuscitation of a patient. Three main issues in patients with exsanguinating hemorrhage are coagulopathy, hypothermia, and acidosis. They are together referred to as the lethal triad and, if not addressed properly, will mutually worsen each other, forming a vicious circle which finally results in the patient's death (6). Additionally, many more factors threaten the patient's condition, all of them connected and influencing each other. The most important ones are discussed in the following.

## 4.1. Trauma induced Coagulopathy (TIC)

Hemorrhages account for 40% deaths caused by Trauma. This makes bleeding control the number one challenge in DCR and therefore is of utmost priority.

As above mentioned, one of the main problems in trauma is coagulopathy, as it severely aggravates bleeding and therefore has to be addressed accordingly.

Coagulation, which amongst others can be triggered by trauma, is an elemental part of physiological inflammatory response processes. However excessive activation may be harmful to the patient due to several reasons. Firstly, it will induce Systemic Inflammatory Response Syndrome and increase the susceptibility for sepsis. Additionally, uncontrolled nonsurgical hemorrhage due to depletion of coagulation factors may lead to early termination of life-saving operations. To preserve life, surgeons are forced to put up with possible loss of limbs or organ failure due to hypoperfusion in patients, which are hemodynamically unstable due to uncontrollable hemorrhage. Additionally, coagulopathy may lead to intracranial hemorrhage leading to neuronal damage which aggravates outcome in traumatic brain injury (1). In fact coagulopathy presents in 25% of trauma patients with base deficit more than 6 at referral (3) and increases the mortality rate in trauma patients up to four times (1).

Coagulopathy of Trauma was earlier believed solely to be caused by resuscitation, hemodilution and hypothermia (3). Now it is understood to be far more complex and well-recognized as complex interaction between shock, tissue trauma, hemodilution, acidemia, hypothermia and inflammation. The amount of damaged tissue in traumatic injuries does not necessarily correlate with the likelihood for developing coagulopathy. Patients with large amounts of tissue damage as e.g. in crush injuries may develop coagulopathy as well as patients with minimal amounts of tissue damage as e.g. seen in stab wounds. By far more important than type of injury is its severity and amount of hemorrhage.

## 4.2. Tissue Trauma and activation of clotting cascade

In coagulopathy of trauma the extrinsic clotting pathway is the dominant driver of coagulation. The intrinsic pathway acts as an accessory to it (7). Excessive activation might result in a hypercoagulative state followed by impaired clotting due to clotting factor consumption. In the extrinsic pathway, trauma causes tissue damage which exposes subendothelial tissue factor (TF). Inactive factor VII (FVII) is floating free in the plasma and forms complex with TF when exposed to it. The FVII/TF complex autocatalyzes and activates itself to FVIIa/TF complex. which activates small amounts of factor X to Xa and factor IX to IXa. Factor Xa together with cofactor V/Va convert limited fractions of prothrombin to thrombin. Thrombin causes platelet activation, initiation of clot formation and further activation of factors V and VIII. This activation of small amounts of thrombin is called initiation phase of thrombin generation.

It is proposed that in this early phase of coagulation activation thrombin levels are so low, that inhibitors in plasma like antithrombin III and tissue factor pathway inhibitor prevent fibrin formation. In the propagation phase of thrombin formation the interplay of factor Xa with factor IXa, cofactor VIIIa, Ca2+ and acidic phospholipids leads to the activation of prothrombinase causing a downright burst in thrombin formation in amounts large enough to eventually cleave fibrinogen to fibrin further promoting clot formation. (8) On the other hand thrombin is a key player in the activation of Protein C, meaning that thrombin does not only promote consumption of clotting factors by activating clotting cascade, but when activated uncontrolled will also participate to development of coagulopathy by inhibiting clotting. (7) This issue is explained in more detail further below.

An important consideration is that due to an amplifying systems on the surfaces of activated platelets, the required amount of tissue factor to activate the clotting cascade is relatively low (1). This explains, why also injuries with small amounts of tissue damage can trigger the coagulopathy of trauma.

This uncontrolled activation of clotting cascade leads to depletion of coagulation factors and greatly contributes to impaired hemostasis in coagulopathy of trauma.

### 4.3. Shock and coagulopathy

Shock is the most important driver for coagulopathy especially within the immediate postinjury phase. The degree of coagulopathy can be measured by determining prothrombin time (PT) and partial thromboplastin time (PTT) which's values at admission correlate with severity of tissue hypoperfusion. In fact, it was observed, that patients without shock tended to show normal coagulation even when suffering from severe injuries. Despite general opinion, platelet counts showed to be at rather normal levels (9).

Our understanding of pathomechanisms behind the relation between shock and coagulopathy is by far not complete. One factor, which will be explained in more detail further below is believed to be connected to acidemia occurring in states of shock. However, this can only be part of the explanation, as coagulopathy in patients with shock was also observed in degrees of acidemia too mild to cause significant deficit in protease activity to impede coagulation factor complex function therefore driving coagulation (1). Coagulopathy at this early stage showed to occur without the finding of coagulation factor depletion (9). There is some evidence, that in acute traumatic coagulopathy with increased base difference due to hypoperfusion in shock, thrombomodulin levels increase. Thrombomodulin forms complexes with thrombin, which

cleave and therefore activate protein C. Protein C inhibits coagulation factors V and VIII and in this way induces coagulopathy (9).

However, some studies presented data on trauma patients presenting in procoagulant state rather than with coagulopathy. This could be explained by protein C depletion (9), but further research on this topic would surely be useful to get a better understanding on the complex mechanisms behind coagulopathy in trauma patients. What can be determined is, that coagulopathy of trauma is accounted for by shock and concomitant hypoperfusion especially in the immediate postinjury phase, and will from there get exacerbated further by other physiological derangements as well as persistent bleeding and the consequences inadequate resuscitation. (1)

### 4.4. Hemodilution

Hemodilution is another important factor, when it comes to coagulopathy in trauma patients. It is caused mainly by fluid shift and fluid resuscitation. To cope for the drop in intravascular pressure, in a state of shock fluid shifts from intracellular and interstitial spaces into the plasma. Consequently, plasma clotting factor levels are diluted. This will further be exacerbated by aggressive intravenous fluid resuscitation with colloid resuscitation fluids. Erythrocyte concentrates yield the same danger.

Additionally, certain types of fluids used in resuscitation might actively influence coagulation in a negative way. There for example is evidence, that administration of normal saline causes hyperchloremic acidosis, which as further explained down below worsens coagulopathy and could even lead to multiple organ failure. The use of hypertonic saline solution has shown to decrease the necessary amount of resuscitation volume in treatment of head and penetration injuries respectively but could still be connected with increased blood loss and mortality. Colloid fluid resuscitation combats the problem of coagulation factor dilution by drawing water from tissues into the circulation and therefore limiting the amount of infused fluid. Nonetheless, at certain amounts colloid fluids were found to negatively influence coagulation and impair platelet function. (7) More information on how to correctly dose fluid resuscitation is provided down below in the section about treatment of coagulopathy.

### 4.5. Hypothermia

The range for temperature that is considered normal is between 35,6°C and 37,8°C. Hypothermia is defined as core body temperature dropping under 35°C. The regulating center of body temperature lies within the hypothalamus. In this brain area information about body

temperature is integrated and processed. If the temperature falls outside the given normal range, mechanisms for loss of heat, like sweating or mechanism for maintaining and producing heat, like muscle shivering are induced. A key player in the regulation of body temperature is blood flow. In case of low body temperature blood absorbs heat produced in muscles and distributes it to the tissues with the highest need.

Hypothermia in trauma patients can be induced by several mechanisms. A patient might lose heat, while being entrapped during an accident in a cold environment. Additionally, the medical rescue team will remove the patient's clothes onsite for a proper bodycheck. The intravenous administration of non-heated fluids will further decrease the body temperature and due to hypoperfusion as well as exhaustion, muscles will produce less heat. Lastly, blood loss will aggravate hypothermia directly by further heat loss and indirectly by hindering redistribution of heat.

It is shown, hypothermia can induce a stress response, resulting in increased discomfort as well as anxiety and pain. Additionally in hypothermic state the oxygen dissociation curve is shifted to the left, meaning that oxygen is less easily released into the tissue. Hypothermia reduces cardiac output and might even cause arrhythmias. The optimal temperature for coagulation factors is 37°C. A body temperature below will impair coagulation and therefore is an important factor in the pathogenesis of coagulopathy of trauma. Additionally, hypothermia has a negative effect on several other non-enzymatic key players of hemostasis as for example Von-Willebrand-Factor, which facilitates blood loss even more. (6)

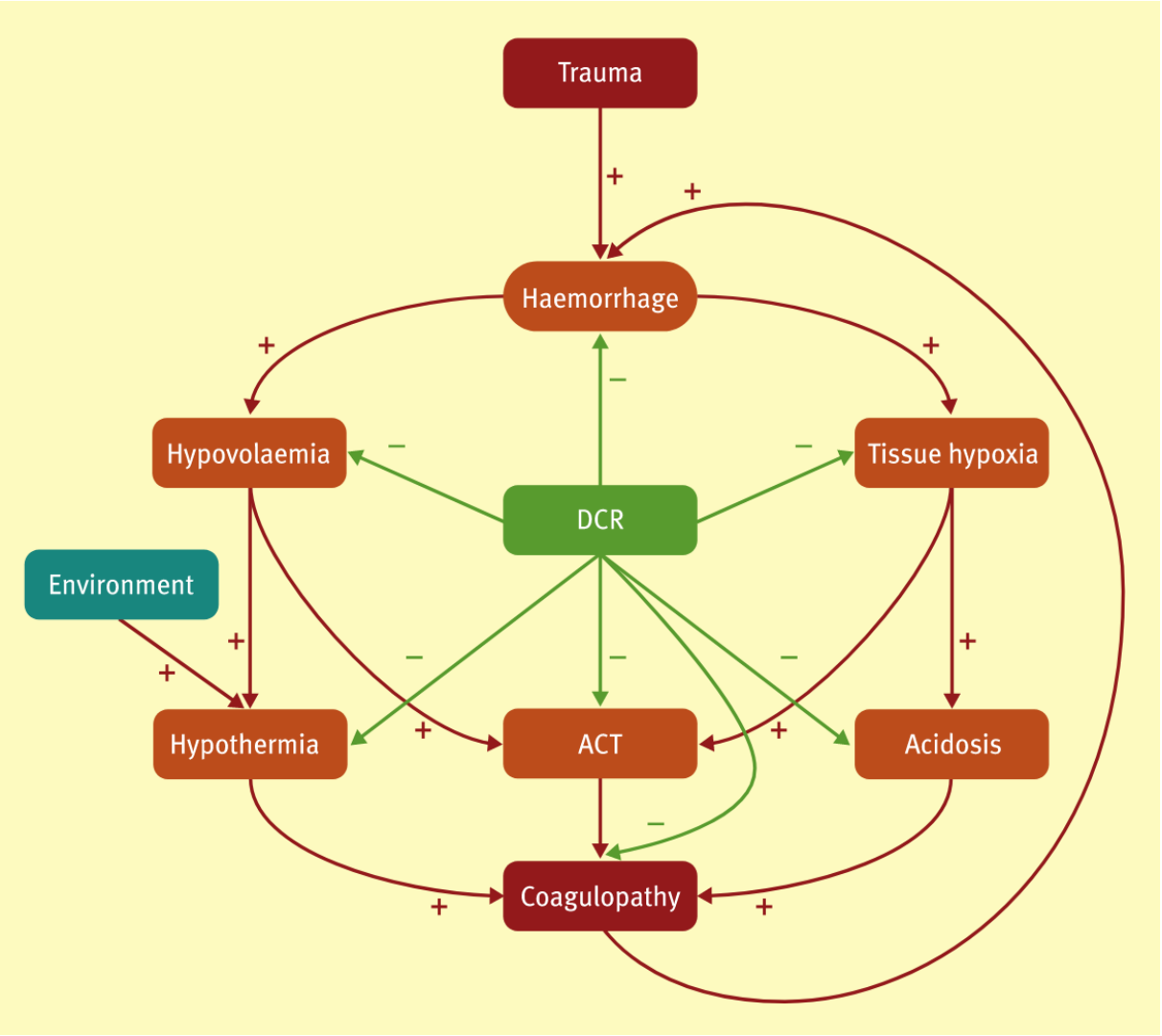
### 4.6. Acidemia

Acidemia is very frequently seen in severe trauma. It is caused by low tissue blood flow in shock and by excessive administration of chloride ions with unbalanced infusions like NaCl 0,9% during resuscitation. Acidemia reduces the function of plasma proteases. This leads to reduction in function of coagulation factor complexes. As an example, to demonstrate the severity of this effect: The action of factor Xa/Va complex at a pH of 7.2 is diminished by 50%, at a pH of 7,0 by 70% and at a pH of 6.8 by 90%, emphasizing how important the correction of acidosis in trauma is.

Additionally, fibrinogen degradation is increased at lower pH levels. This will result in decreased stability of blood clots. Decreased action of coagulation factors as well as fibrin plug destabilization in an acidotic state are the two important mechanisms, how acidemia contributes to coagulopathy in trauma patients. It seems, that the administration of buffer solutions to combat acidemia, helps in raising pH but fails to correct coagulopathy. This is believed to be

due to different overlapping mechanisms which all take part in induction of coagulopathy (1). Further management of coagulopathy is discussed down below.

Figure 1. Simplified process of traumatic coagulopathy and damage control resuscitation (2)




## 5. TREATMENT

Damage control resuscitation aims to comprehensively combat all afore mentioned pathophysiological elements of a trauma patient's critical state secondary to severe hemorrhage, acidosis, and hypothermia. The period until definite surgical hemostasis is established, can be subdivided into three phases based on the setting and hemostatic measures performed (10).

The first phase refers to the time span from the injury until medically trained personnel arrives. The setting usually is at the site of injury and medically not skilled first responders usually have limited means. Hemorrhage sometimes can be controlled using band aides or by simply

applying pressure to the wound, but these measures quickly reach their limits, especially when it comes to internal hemorrhages, or large diffuse bleedings. In case of circulatory arrest, Cardiopulmonary Resuscitation (CPR) is indicated.

The second phase is marked by the presence of medical personnel and includes the transport from the site of injury to the hospital. Fast hemostatic measures include packing wounds or clamping vessels as well as the application of tourniquets or ligatures and can help to drastically decrease blood loss. Nonetheless, especially in critically wounded patients with severe blood loss, Prehospital Trauma Life Support guidelines dictate the delay of further time-consuming resuscitation measures in favor of immediate transport to a medical facility, also known as scoop and run approach. This is of even greater importance in a setting, where the number of patients exceeds the capacities of the rescue forces onsite. (10)

The third phase describes the in-hospital management before operative treatment of the trauma patient and from the perspective of hemorrhage management the main measures can be grouped under the key terms permissive hypotension, massive transfusion administration, hemorrhage control, coagulopathy management, hypothermia treatment and correction of acidosis (11). It is crucial to understand, that these measures only aim to stabilize the trauma patient. Urgent definite surgical hemorrhage control might very well be its only chance for survival.

There are several tools that help with assessment of the patient. By assigning certain physiological factors a measurable number, physical status of the patient is quantified. Based on these values a certain therapy can be introduced.

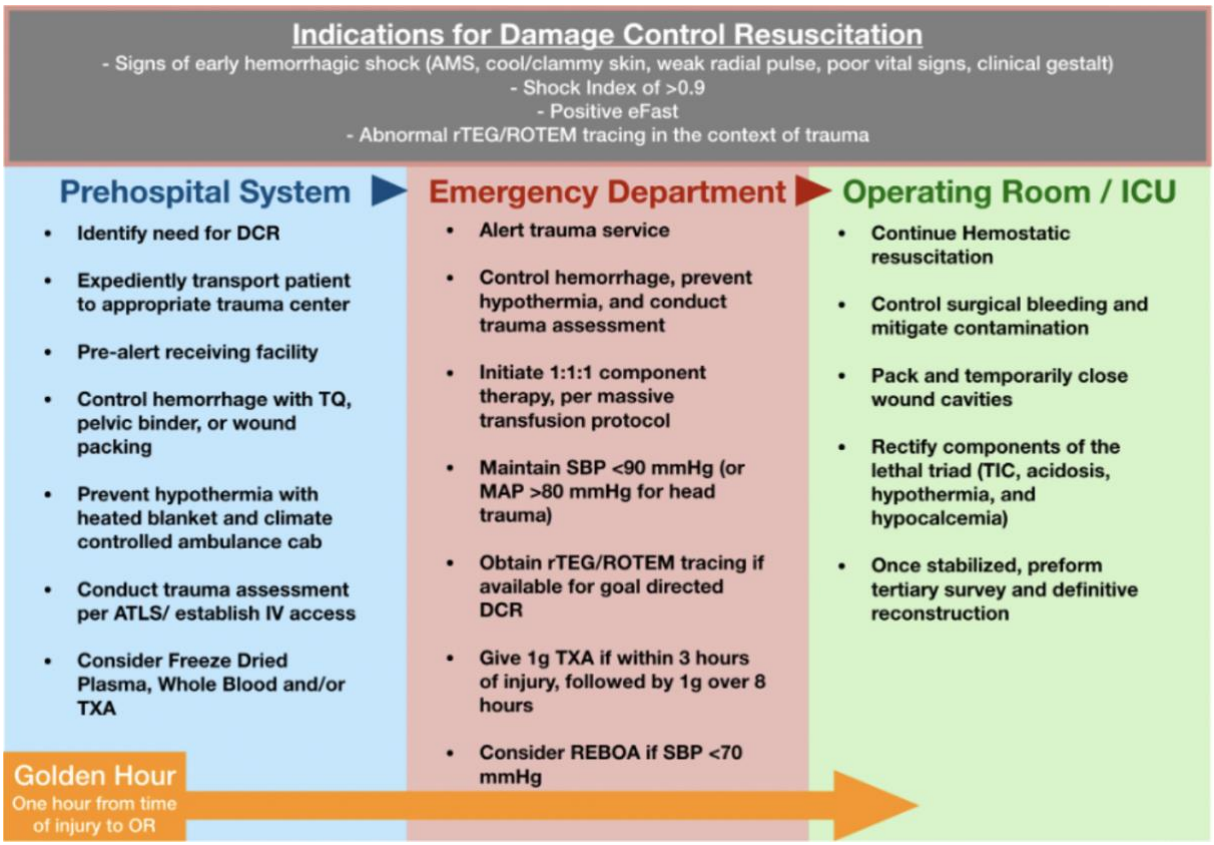
An important system is the Glasgow Coma Scale (GCS). It measures the patient's level of consciousness by assigning certain set of possible points to eye opening (max. 4), motor response (max. 6), and verbal response (max. 5). The GCS is especially useful in assessing severity of TBI. A patient with the highest GCS value of 15 is fully awake and responds adequately. Values between 13-15 can be expected in concussion. GCS 9-12 implies moderate TBI and GCS 3-8 makes severe TBI very likely and indicates immediate intubation.

Even though GCS does not replace a detailed neurological exam, in emergency situation like severe trauma, where time is a critical factor, it is a powerful tool, to make quick evidence-based medical decisions.

There are several other assessment tools to determine the patient's status and severity of injuries. The Revised Trauma Score (RTS) is used to estimate chances for survival based on RR, systolic BP, and GCS. The Injury Severity Score (ISS) cumulatively quantifies injuries based on location (head/neck, face, chest, abdomen, extremities, external injuries) and severity (1 mild – 6 maximal).

ISS and RTS combined form the Trauma and Injury Severity Score (TRISS), which is mainly used for quality control and for research purposes in trauma patients. (12)

Figure 2. DCR and the chain of survival (13)




## 5.1. Permissive Hypotension and fluid resuscitation

Permissive hypotension is the term used for maintaining blood pressure levels in a patient with ongoing hemorrhage lower than the physiological values by limiting the amount of fluid resuscitation. While increasing the risk of hypoperfusion, this potentially evades adverse effects of forced fluid resuscitation which are further elucidated down below. The recommended targeted systolic blood pressure is 80-90 mmHg. It is important to notice, that the concept of permissive hypotension is not indicated in patients with trauma to the spine or traumatic brain injury. This is due to the particular dependence of damaged neural tissue on proper perfusion to maintain adequate oxygenation to avoid secondary brain or spinal cord damage (11). In trauma patients with damage to these particular regions the recommended systolic target pressure is 110 to 120 mm Hg.

It is believed, that in severely hemorrhaging patients treated with aggressive fluid resuscitation, increased hydrodynamic forces due to higher flow velocity and increased blood pressure negatively influence formation and stabilization of thrombi. Restrictive fluid resuscitation is

recommended, with small amounts of fluids between 150 and 250 ml to keep blood pressure in the range of permissive hypotension strategy. Usually, 500 to 750 and no more than 1000 ml of balanced crystalloids should be administered intravenously before surgical emergency procedures. More excessive fluid resuscitation will cause even more hemorrhage due to thrombus destabilization, requiring more fluid resuscitation and finally resulting in a kind of viscous circle. Additionally, rapid volume replacement might reverse peripheral vasoconstriction and therefore contributes to increased hemorrhage and hemodynamic destabilization.

Besides the fact that it should be dosed wisely, the type of intravenous fluid utilized for resuscitation in trauma patients plays an important role. When infusing crystalloids, there is evidence that balanced crystalloid solutions have a better outcome over unbalanced solutions, as their chloride ion concentration is similar to the one of human plasma and they contain buffers. In unbalanced colloids like saline, the amount of chloride ions in relation to sodium ions is higher. Saline infusions of more than 1000-1500ml might induce or worsen existing acidosis, which as above mentioned is one part of the lethal triad in trauma patients. This is why unbalanced crystalloids are contraindicated in patients with severe acidosis especially in the presence of hyperchloremia. An additional aspect to be careful about when it comes to crystalloids in damage control resuscitation is, that hypotonic solutions like Ringer's lactate should not be used in TBI as they pose an increased risk of fluid shifting into damaged cerebral tissue.

Another valid option is the use of colloids. Their advantage lies within their increased colloid-osmotic pressure. For their ability to keep fluid in the circulation they are also called plasma expanders. They are more effective than crystalloids in restoring intravascular volume in hypovolemic conditions. Additionally, their half-life in the circulation is longer than the one of crystalloids. Nonetheless colloids have a row of adverse effects, which makes it important to use them with caution. For example, HES 6%, the most common colloid, is nephrotoxic and can induce anaphylactoid reactions as well as coagulopathy, which given the pathophysiological mechanisms is especially unfavorable in trauma patients. That is why colloids are rather indicated as an additional treatment in severe hemorrhage, if basic tissue perfusion cannot be met under the influence of crystalloids in combination with vasopressors (14).

## 5.2. Transfusion

Besides volume restitution with balanced crystalloids and colloids, the transfusion of blood products is very helpful in stabilizing the patient as they additionally have the capability to

increase oxygen transport and combat the effects of coagulopathy. Blood components that can be transfused are packed red blood cells (pRBC), fresh frozen plasma (FFP) and thrombocytes. When it comes to erythrocyte transfusions the recommended target hemoglobin level is 70-90 g/dL (14). It is crucial to keep in mind that in acute hemorrhage, the hemoglobin level initially does not reflect the severity of blood loss and therefore should not alone be used to make the decision for a transfusion. Additionally, severity of the wounds and most importantly the clinical appearance of the patient are indicative. As hemorrhagic shock can evolve rapidly it is important to anticipate a possible necessity for transfusion. It is preferred to transfuse pRBC of the same blood type. But when indicated, transfusion should not be delayed in favor for blood group determination, crossmatching and ordering it from the blood bank. Instead, 0 negative pRBC units should be used. In case of severe hemorrhage, as in DCR, massive transfusion might be indicated. Massive transfusion is defined as a treatment regime with ten or more units of pRBC within a period of 24 hours. As this definition is not useful in the acute treatment of hemorrhage, additionally the use of more than 4 units of pRBC in on hour, when ongoing need is likely, or the replacement of more than half of total blood volume within 3 hours is proposed. Massive transfusion builds the foundation for activation of Massive Transfusion Protocols (MTP). An MTP is a treatment regime, that usually is activated after transfusion of 4-10 pRBC units in patients with fast physiological exhaustion due to ongoing hemorrhage. It additionally to erythrocyte transfusions contains the transfusion of units of FFP and platelets in the ration of 1:1:1 or 1:1:2. Once the protocol is initiated, the fast delivery of all blood components together are provided by the blood bank, which facilitates resuscitation and makes communication between blood bank and physician easier and less time consuming (15). MTP may lead to remarkable improvement in a severely injured patient's condition and might even enable surgeons to carry out complete surgical interventions instead of just performing DCS as for example leaving the abdomen temporarily open (3). Additionally, it was shown that the implementation of MTP leads to the earlier use of blood products during resuscitation and increases the efficiency of blood banking systems. It helps in decreasing overall number of blood products during hospital stay and leads to significant economic savings. Additionally, massive transfusion leads to a decrease in excessive administration of crystalloid fluids (3). Outside of MTP, the administration of platelets is induced in trauma patients with persistent hemorrhage to keep the platelet count above $50x10^9$ or $100x10^9$ in case of TBI. The suggested initial dose is four to eight units of platelets.

## 5.3. Coagulopathy management

Coagulopathy in trauma patients can be combated by correcting the above-mentioned pathophysiological processes. Additionally, coagulation can be actively promoted, and fibrinolysis can be actively inhibited.

A start of the treatment with the antifibrinolytic agent tranexamic acid (TXA) in trauma patients with severe bleeding or risk for severe bleeding is indicated as soon as possible but latest 3 hours after the injury. Even the administration already on the transport to hospital can be considered, if feasible. The recommended dose is 1g within the first 3 hours after injury as an infusion over 10 minutes followed by another 1g over the next hours. Viscoelastic hemostatic essays can be used to further elucidate coagulation and fibrinolysis status but TXA treatment should not be delayed in favor of waiting for results (4). Additionally, FFP therapy in ratio 1:1 with pRBC might be beneficial as it contains all coagulant factors. (14) Nonetheless their concentration is only about 70% of normal plasma levels, and there is evidence for FFP transfusions being a risk factor for mortality or worse functional outcome especially in TBI (16). In general, if a coagulation resuscitation strategy based on FFP is used, it should be guided by coagulation screening parameters (PT or APPT > 1.5).

Additionally, point-of-care laboratory testing like thromboelastography (TEG) and the more advanced rotational thromboelastometry (ROTEM) has shown to be useful in diagnosing acute traumatic coagulopathy as well as determining its severity. These devices allow assessment of dynamic processes of coagulation, that is to say clot formation, propagation, stabilization and finally clot dissolution (17). This enables the introduction of more targeted treatment regimens based on coagulation factor concentrates.

One of the most important coagulation factors to substitute is fibrinogen. Fibrinogen levels under 1.5 g/L are considered critical and are commonly seen in severely injured patients at admission. FFP is not well suited to raise fibrinogen levels above 1.5 g/L as fibrinogen levels of therapeutic plasma are around 2 g/L, which increases the required plasma volume exponentially, when fibrinogen levels raise above 1.5 g/L. Additionally FFP transfusion cannot be initiated simultaneously to pRBC. Therefore, to initially support coagulation even while awaiting laboratory results, under certain circumstances, it is proposed to administer 2 g of fibrinogen together with the first 4 pRBC units to imitate a 1:1 ratio between pRBC and plasma and battle a possible hypofibrinogenemia. Criteria for induction of a fibrinogen concentrate therapy are systolic BP < 100 mmHg, lactate ≥ 5 mmol/L, base excess ≤ -6 or Hb ≤ 9 g/dL. In case of normal fibrinogen levels, the use of prothrombin complex concentrate (PCC) is recommended. It is interesting to note, that PCC is advantageous over FFP when it comes quick

counteraction of vitamin K antagonists. Nonetheless PCC use should be used deliberately as it increases thrombin potential for several days and with it the risk for thrombotic complications. Another important clotting factor that has shown to be important for thrombus stability is FXIII (18). Therefore, it is reasonable to substitute FXIII, should the level fall under a certain value. However, an exact number for this threshold value has not been officially determined yet. In the guidelines for management of severe perioperative bleeding from the European Society of Anesthesiology, the recommendation is to start treatment with FXIII in a patient with ongoing bleeding and a FXIII activity under 30% (19). Even though this guideline is not specific to trauma patients, this value seems to be a reasonable reference value to base a possible FXIII concentrate therapy on in DCR.

Another challenge in coagulopathy management is if the patient is using some kind of antithrombotic therapy. The use of vitamin K-dependent oral anticoagulants should be suspected, if a history of atrial fibrillation, previous thromboembolism or a mechanical heart valve is known. In this case the immediate treatment with both PCC and 5-10 mg, iv. of the vitamin K1 compound phytomenadione is advised. The target is to achieve normal INR values as soon as possible. When choosing the kind of PCC, four-factor PCC, if available, should be chosen over three-factor PCC, as they contain an higher amount of FVII in relation to the other coagulation factors, which is beneficial in restoring INR (19,20).

When it comes to reversing the effects of a possible direct oral anticoagulant treatment, patients with life-threatening hemorrhage who received treatment with dabigatran, should be treated with idarucicumab, 5mg, iv.

The use of platelet transfusions to reverse of effects of an antiplatelet treatment prior to the injury is not recommended.

Finally, it is to be mentioned, that despite the effort to combat coagulopathy, thromboprophylaxis should be initiated early. In immobile patients with an increased risk for hemorrhage, this is achieved by intermittent pneumatic compression (IPC). 24 hours after definite control of bleeding, a combination of IPC and pharmacological thromboprophylaxis should be started until the patient regains mobility (19).

### 5.4. Vasopressor treatment

In response to severe hemorrhage, the body initially reacts with hyperstimulation of sympathetic nervous system. In this early symphathoexitatory phase, enhanced vasoconstriction and increased heart rate contribute to an at first relatively stable blood pressure. But with progression of hemorrhagic shock sympathetic response will decrease up to a downright

sympathoinhibitory state with vasodilation and bradycardia resulting in destabilization of blood pressure (21). In this late phase introduction of vasopressors is a useful option in the treatment of hypotension due to hemorrhage. Vasopressor treatment is indicated, if a systolic blood pressure over 80mmHg cannot be maintained by restrictive fluid resuscitation alone. Nonetheless, as explained above in the section about permissive hypotension, the targeted systolic blood pressure should not exceed 90mmHg and vasopressor dose has to be adjusted to keep the systolic blood pressure in that 80-90mmHg interval.

If blood pressure is not or only poorly responding to fluid and vasopressor treatment, myocardial dysfunction as e.g. due to cardiac contusion or pericardial effusion has to be suspected. In this case treatment with inotropic agents as adrenalin or dobutamine is advised.

Based on the hypothesis, that hemorrhagic shock is associated with deficiency in vasopressin, the possible benefits of vasopressin supplementation are currently under investigation. But further research is necessary to make a recommendation regarding that treatment option (14).

### 5.5. The Role of Calcium

Calcium cations play an important role in coagulation. Their role is to enhance the function of coagulation factors by acting as a positively charged bridge between negatively charged coagulation factors and the negatively charged phospholipids of the endothelium. Additionally, it aids in the conversion of prothrombin to thrombin and fibrinogen to fibrin. Furthermore, it has been discovered that low intracellular calcium levels are associated with decreased platelet activity, as calcium partially mediates platelet integration into the thrombus (22). Ionized hypocalcemia is also associated with decreased contractility of the heart, as in a hypocalcemic state, the release of calcium within cardiac myocytes is limited. Especially in patients who received treatment according to MTPs are at increased risk of developing severe hypocalcemia. Severe hypocalcemia is directly related with the number of transfused units of pRBC and is a significant risk factor associated with mortality. (23) These all are reasons, why it is important to keep calcium levels within normal levels. An ionized calcium level of 1.1-1.3 mmol/L is considered normal, and it is dependent on the pH. With every pH increase by 0.1 units, calcium concentration will decrease by 0.05 mmol/L approximately.

For treatment of hypocalcemia it is recommended to administer calcium chloride as 10ml infusion of 10% solution. (14)

## 5.6. Hypothermia treatment

As mentioned above, hypothermia has a negative effect on coagulation and other hemostatic processes and it is known, that there is a link between hypothermia at the time of admission to hospital and a decreased survival rate (6). That is why it is of great importance to treat hypothermia accordingly or even better to prevent it in the first place.

A first step is to remove all wet clothing from the patient. Additionally, an increased ambient temperature is helpful to prevent further heat loss. Fluids for resuscitation should be heated before administration. When it comes to covering the patients there are several options. Rescue blankets are a very good option as they provide a high grade of insulation. But if they are not available conventional materials are better than nothing. Another reasonable options especially in the field is the use of a hypothermia prevention and management kit. (19) These kits were originally developed for hypothermia management during casualty evacuation scenarios in the military but also find use in civilian settings. These bags with an inbuilt hood are lightweight, relatively inexpensive and consist of resilient shell fabric, with a non-conductive, heat reflecting layer, that provides excellent insulation. Four oxygen activated heat sources, that do not rely on external power supply, sustain up to 10 hours of dry heat.

In a hospital setting active heating can be achieved by the used of mechanical heating devices. The use of heat packs is a valid option as well.

## 5.7. Correction of acidosis

The etiology and harmful effects of acidosis in trauma patients have already been discussed above. The normal pH value in a healthy individual is tightly maintained in the range of 7.35-7,45. Higher values indicate alkalosis, while lower levels indicate acidosis. Alkalosis as well as acidosis can have metabolic, respiratory, or mixed origin. In case of severe hemorrhage, acidosis is of metabolic nature. Levels below 7.30 are considered severe acidosis and levels below 7.20 are considered critical (24). The most important aspect of dealing with acidosis is the correction of physiological imbalances causing it, which means restoring oxygen supply to the tissues by oxygen treatment, adequate fluid resuscitation while keeping in mind the permissive hypotension principle and blood product treatment. Additionally, it is common practice to administer bicarbonate therapy to further combat acidemia. However, in the last years its usefulness has become subject of investigation. There are studies that suggest that bicarbonate treatment in trauma and severe acidosis might even harm the patient.

Amongst others, sodium bicarbonate showed to increase the patient's $PaCO_2$ as much as 5mmHg per administered 50mEq. Especially in rapid administration, the quick $CO_2$ build up

might exceed the bodies clearance capabilities resulting in $CO_2$ crossing into tissues including the brain. Furthermore, despite increasing arterial pH, bicarbonates might decrease pH in other tissues like brain, muscles, and liver (25). Scientific data to this day is ambiguous. Nonetheless, the bicarbonate treatment yet is found in several guidelines and its use remains controversial.

## 5.8. Intermittent on-site hemorrhage control measures

When it comes to the treatment of critically wounded patients with severe hemorrhage, surgical control of the bleeding might well be the patient's only chance for survival.

There are several surgical measures and techniques to address hemorrhage. Some are rather complex and are performed by highly trained personnel, others do not even require an operating room and can be performed as temporary measures at the site of injury. Putting DCR into this context, it aids to stabilize the patient on the way from the scene of injury to the hospital, during and after DCS. The next section discusses some of the commonly used procedures.

Most often, in a civilian setting even life-threatening hemorrhage will be manageable by simple compression of the wound. This can be done already at the site of injury either by applying pressure manually or by using pressure bandages (19). These bandages are even more effective when used in combination with local hemostatic agents (26). More forced and targeted compression can be achieved by the use of balloon catheters. This is explained in more detail down below.

In severe injury to extremities and especially in scenarios where the number of heavily injured patients exceeds the capacities of the available medical personnel, the use of tourniquets can assist in quickly stopping severe hemorrhage temporarily, until definite wound management can be achieved.

Another way of achieving hemostasis is the Abdominal Aortic Tourniquet (AAT). This device is used in injuries, in which hemorrhage control cannot be achieved by the use of a regular tourniquet as for example high traumatic leg amputations or injury to the scrotal area. The device comprises of a circumferential abdominal strap, with a wedge-shaped balloon, that upon inflation arrests blood flow in the abdominal aorta distal to the height of the umbilicus.

Even though AATs are at this time mainly applied in military settings, it is believed, that their application could be of significance in civilian trauma care as well. (27)

## 5.9. Vascular Damage Control Techniques

Vascular damage control techniques count to the most important measures in damage control as the aim to stop bleeding from large vessels and are therefore very effective in preventing further deterioration of the patient's status. Traditionally, these techniques were limited to simple ligation of the injured vessel, resulting in two major issues. Firstly, ligations can only be performed, if the source of the bleeding can be identified and properly accessed. Diffuse bleedings or hemorrhage from vascular structures deeply seated in the wound-track will present difficult to control that way. This is why newer methods from different fields of medicine were implemented in a way to fit the demands of damage control.

### 5.9.1. Balloon catheter tamponade

Originally used as a hemostatic agent in the treatment for esophageal varices, balloon catheter tamponade soon proved to open a variety of possibilities in management traumatic vascular damage and organ injuries. It is relatively easy to perform and is nowadays amongst others used in trauma to the heart and aorta, abdominal trauma to vascular structures and the liver as well as trauma to face and neck. Depending on the kind of injury, the balloon can either be placed through a vessel or it can be introduced directly into the wound next to injured vessel or organ structure. It is then inflated with air, therefore applying pressure to the surrounding structures in this manner facilitating hemostasis.

Nowadays the use of balloon catheter tamponade is only of limited importance, as standard measures for hemorrhage control are pretty effective. Nonetheless it can be used in situations in which applying pressure to the wound is not possible due to inaccessibility as e.g. in deep open abdominal wounds. Another possible scenario are injuries, where application of a tourniquet is not possible. Additionally balloon catheter tamponade is used if major vessels are damaged as well as in deep parenchymal bleeding of solid organs e.g. liver or lung (3).

A special type of balloon catheter tamponade is Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA). It aims to temporarily occlude the lower part of Aorta to increase central or proximal perfusion towards the heart. Even though it shows possible benefits over traditional laparotomic clamping of aorta, this technique is not as well implemented as it could be. Especially in the treatment of vascular diseases with severe hemorrhage like the rupture of an abdominal aortic aneurism, the use of REBOA is a valid option. Access is gained through the femoral artery (28).

### 5.9.2. Temporary Intravascular Shunt (TIVS)

TIVSs are intraluminal tubular devices which aid in temporarily maintaining blood flow through a vessel. These shunts are developed to either bridge an acutely occluded vessel causing ischemia of body parts distal to vascular obstruction especially if distal organs or limbs are in danger; or to bridge a vessel damaged during trauma, maintaining perfusion of tissue distal to the interruption while simultaneously stopping hemorrhage. Especially in trauma these procedures are often life and limb -saving (3). They are used in large arterial injury and extensive soft tissue damage in open fractures on extremities as well as control of severe peripheral vascular damage.

There is a rising trend of use of TIVS in military and civilian medicine. The two main goals of TIVS are to reestablish perfusion to enable orthopedic fixation, and to quickly deal with bleeding so attention can be paid to other injuries or physiological derailments.

Additionally, TIVS is applicable to stabilize a patient for transport to a facility with an appropriate trauma center, in locations without the means to establish definite treatment to a vascular injury. In military setting practically all the performed shunts are used for damage-control to enable safe transport to higher-level care facility. In the civilian sector still over 50% of shunts are used for damage-control purposes.

In a damage control setting, a variety of medical equipment can be alienated and used as an intermediate shunt. Chest tubes are commonly used to bridge larger damaged vessels but sometimes even feeding tubes are utilized (29).

As possible side effects of TIVS compartment syndrome, tissue hypoxia and even necrosis have been described. The most frequently reported complication though is thrombosis which was observed in about 20% of patients in military setting and 7% of patients in a civilian setting (3). The use of systemic heparinization in TIVS to combat thrombosis is still controversial.

Most of TIVS remain in the patient no longer than 24 hours. But a study (30) showed, that in selected patients, shunts could stay open and deliver sufficient blood supply to the severed limb for up to 52 hours without anticoagulation. In fact, one case is described, where a shunt remained patent for 10 days in an axillary artery without systemic heparinization. This nonetheless is to be attributed at least partially to trauma-induced coagulopathy present in the patient after severe injury (29). In general the use of TIVS has been shown to improve outcome for effected limb due to early restoration of blood flow (31) and decrease the need for amputation of the affected limb (3). Salvation of the limb depending on sources was achieved in between 80% and 90% (31) or even near to 100% (29). The highest mortality in patients who received TIVS was observed with the use of non-extremity shunts.

### 5.10. Damage control surgery

As explained in the beginning, DCS is a relatively old concept. It can be described as a kind of abbreviated laparotomy, that prioritizes physiological recovery over anatomical restoration. Together with the newer concept of DCR it forms the field of Damage Control. It is important to understand that a patient is not treated with either DCS or DCR. Much more these two concepts are used synergistically to achieve definite hemostasis, while simultaneously correcting the patient's physiological derailments. To maximize the effectiveness of the Damage Control process, it is structured in a 4-step process (DC 0-DC III) based on the chronological order of the different measures.

## 6. DAMAGE CONTROL PROCESS

### 6.1. DC 0

This phase is the earliest in DC, starts with pre-hospital medical care and continues in the Emergency Department. The main goal is to identify injury patterns and to determine, whether the patient will benefit from damage control treatment. The afore explained scoop and run strategy, is part of that phase as an important measure. Choosing and timely informing an appropriate hospital with an adequate trauma care center is of great importance. Additionally, the early use of TXA has been promoted in this phase, lately.

At arrival to the hospital all patients should immediately receive at least one, better two large bore iv. accesses and Rapid Sequence Intubation if not already performed, as well as chest drainage, if needed. DCR is started immediately, and the patient is to be transported as soon as its condition allows it. It is important to communicate the need for an operating room in advance to enable the possible preparation of cell-savage devices and the needed instrument trays.

### 6.2. DC I

In this phase emergency laparotomy or other lifesaving operative procedures are performed. The main aims are to control hemorrhage, to limit contamination and to then close the abdominal wall temporarily. The goal is to restore physiological function. Anatomical reconstruction is secondary. DCR started in DC 0 is continued in DC I.

The needed medical equipment includes a cell-saver suction device, if available, several instrument trays including a laparotomy set, chest and vascular instruments and a sufficient amount of laparotomy pads to initially perform abdominal packing.

By placing the patient on the operating table in the cruciform position, and by prepping the patient from chin to the mid thighs, access to most of the lifesaving surgical procedures is ensured. Additionally, no ECG leads, or other monitoring equipment should be placed on the anterior and lateral chest to not interfere with sternotomy or thoracotomy or tube thoracostomy. The placement of a urinary catheter as well as a nasogastric tube is imperative.

Surgical access is chosen depending on the injury pattern. In case of an abdominal exploration for example, the incision is made from the xyphoid process of the sternum to the pubic symphysis. After entering the peritoneal cavity large blood clots can be removed manually and by suction. Subsequently, the abdominal cavity is packed, to assess the location and degree of significant injuries. Abdominal packing, if done properly, is mostly sufficient to arrest venous and solid organ hemorrhage. In case of large venous or arterial lesions, transient hemorrhage control can be quickly achieved by either manually compressing or clamping the abdominal aorta at the diaphragmatic hiatus. This buys the anesthesiologists time to stabilize the patient and clears the visual field for surgical damage control. Great vascular injuries as mentioned above can either be managed by vessel ligation or by temporary intravascular shunt placement. Major damage to spleen, kidneys or pancreatic tail is usually best managed by partial or total resection. Injuries to the liver are managed either by packing only or if not sufficient, by temporarily disrupting blood inflow at the level of the portal vein.

To address the risk for infection due to intestinal content and urine spilling, simple ruptures can be primarily repaired by suturing or in case of more complex injuries partial resection can be indicated. Additionally, injury to bile or pancreatic duct is temporarily managed by forming a fistula with a tube. As all significant intraabdominal injuries are addressed accordingly, the abdomen is further packed and temporarily closed. Fascial closure is not recommended as it yields the danger of increased intraabdominal pressure and, in the worst case, abdominal compartment syndrome.

DCI is completed, as all hemorrhage is arrested. This might sometimes require additional interventional radiological procedures.

### 6.3. DC II

DC II refers to the phase, where the patient in which surgical hemostasis could just be achieved is now further stabilized on the ICU. DCR here plays an important role in further combating coagulopathy hypothermia and specific measures have extensively been described above. The goal is to achieve normal physiological parameters. How long that takes, depends on the patient and the injury but the usual duration is 24 to 36 hours. Patients during this time receive

unplanned reoperation either in case of missed or inadequately addressed hemorrhage or due to development of abdominal compartment syndrome.

### 6.4. DC III

The last step comprises of measures to perform final abdominal closure. In a first step the abdomen is opened up and all package material is gently removed to avoid blood clot dislodgement. Subsequently, thorough abdominal examination is performed to detect previously overlooked or inadequately addressed injuries. Positive findings are addressed accordingly, and bowel continuity is restored. After all lesions are finally managed appropriately definite abdominal closure can finally be performed. It is indispensable, that the closure is performed without tension to the tissue. If this is not possible due to persistent intestinal oedema, the patient receives a temporary abdominal closure device and is referred back to the ICU. Forced diuresis can help to reduce swelling and regular inspection as well as replacement of the abdominal closure device has to be performed to counteract fistula formation. Mostly definite closure can be achieved within one week from the injury. If definite fascial closure is not achieved by then, the surgeon is forced to use different approaches, which mostly result in large hernias, which should be surgically corrected later. (24) It is to be said that depending on the severity of injuries DCR can sometimes buy enough time to skip DCS in the first place and instead achieve definite surgical wound closure directly.

## 7. CONCLUSION

In conclusion, it can be said that broad topic of Damage Control has been in the focus of medical research for quite a while now. By investigating the complex pathophysiological mechanisms connected with severe trauma, we started to be able to combat the individual influencing factors one by one and made tremendous progress in managing heavily injured patients. Especially the implementation of DCR as an extension to DCS elevated modern medicine trauma care to a whole new level.

But that does not mean that there is not still room for improvement. There are still parts in the pathophysiology of trauma, that we have not been able to fully comprehend in all their complexity. Additionally, plenty pieces of new data on trauma care are collected every year which leaves us with the task to constantly reevaluate our therapeutic guidelines and adept them to the latest scientific findings.

But considering the tremendous personnel expenditure in emergency medicine and given the fact, that the shortage of medical staff is aggravating alarmingly year by year, lack of knowledge

or a deficit in sufficiently advanced treatment techniques might not be the next big challenge in trauma care after all.

## 8. SUMMARY

To sum up, the term Damage Control originates from the British Royal Navy, where it described intermediate emergency measures to bring damaged ships back into their harbor for definite repair. The term nowadays is analogously used in trauma care to describe an emergency treatment regimen for managing severely injured patients with life threatening hemorrhage. Damage Control comprises of Damage Control Resuscitation, which aims to initially stabilize the patient and Damage Control Surgery, which pursues to achieve rapid hemorrhage control in order to maintain the patient's physiological functions, often at the cost of initial correct anatomical restoration.

Three main factors, that is to say coagulopathy, hypothermia, and acidosis, drive the physiological deterioration in trauma patients and are collectively referred to as the lethal triad. Beyond, there are several additional aggravating factors as for example shock and hemodilution. For a sufficient treatment all of them have to be addressed.

Permissive hypotension with blood pressure guided fluid resuscitation is a good way to initially combat hemodynamic instability. Additionally, the use of blood products is a pillar of DCR as it addresses coagulopathy and increases the tissue oxygen supply at the same time. Massive Transfusion Protocols facilitate blood product administration in trauma patients and provide pRBC, FFP and thrombocyte transfusion usually in the ratio 1:1:1. Blood pressure control can further be achieved by the use of vasopressors and coagulopathy of trauma is addressed by the early use of TXA, coagulation factor substitution and $Ca^{2+}$ supplementation. Hypothermia is best approached by covering the patient adequately, warming infusions before administration, and the use of heating devices.

In the end, these measures serve to stabilize the patient, but chances for survival are slim without immediate surgical hemorrhage control. This starts at the site of injury by compression of the wound or the use of bandages and tourniquets. More advanced techniques include Balloon Catheter Tamponades and Temporary Intravascular Shunts. Especially in a combat situation, these measures can be performed even outside an operating room.

For most severe trauma cases, especially in abdominal trauma, Damage Control Surgery is performed before definite surgical treatment. It is important that DCR and DCS act together synchronously. The key to an unimpeded and sufficient management of a heavily injured patient is good communication amongst all members of the medical team at all times.

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## 10. CURRICULUM VITAE

Moritz Rupert Mayr was born on the 4th of December 1996 in Darmstadt, Germany. He started attending Elementary School first in Birkenau and finished it in Murnau am Staffelsee in Bavaria. Here, he also visited the Staffelsee-Gymnasium, from which he graduated in 2015. During his school years Moritz pursued his passions for music by being part of several bands and choirs, and for mountaineering and is still doing so to this day. After completing the Abitur, he spent some time working and then travelled to Chile, before enrolling into Medical Studies in English Language at University of Rijeka, Croatia. After graduating, Moritz Mayr will return to Bavaria to start his specialization in orthopedics and trauma surgery.