Hot Topics in Acute Care Surgery and Trauma

Zsolt J. Balogh · Raul Coimbra · Salomone Di Saverio · Andrew W. Kirkpatrick · Federico Coccolini *Editors*

Postinjury Multiple Organ Failure

Springer

Hot Topics in Acute Care Surgery and Trauma

This series covers the most debated issues in acute care and trauma surgery, from perioperative management to organizational and health policy issues. Since 2011, the founder members of the World Society of Emergency Surgery's (WSES) Acute Care and Trauma Surgeons group, who endorse the series, realized the need to provide more educational tools for young surgeons in training and for general physicians and other specialists new to this discipline: WSES is currently developing a systematic scientific and educational program founded on evidence-based medicine and objective experience. Covering the complex management of acute trauma and non-trauma surgical patients, this series makes a significant contribution to this program and is a valuable resource for both trainees and practitioners in acute care surgery.

More information about this series at http://link.springer.com/series/15718

Zsolt J. Balogh • Raul Coimbra
Salomone Di Saverio
Andrew W. Kirkpatrick • Federico Coccolini
Editors

Postinjury Multiple Organ Failure

Springer

Editors
Zsolt J. Balogh
Department of Traumatology
John Hunter Hos and Univers of Newcastle
Newcastle, NSW
Australia

Salomone Di Saverio
General Surgery Department
ASUR Marche
San Benedetto del Tronto
Italy

Federico Coccolini
General, Emergency and Trauma Surgery Department
Pisa University Hospital
Pisa
Italy

Raul Coimbra
Department of Surgery
Riverside University Health System
Medical Center
Moreno Valley, CA
USA

Andrew W. Kirkpatrick
Department of Surgery and Critical Care Medic
Foothills Medical Centre
Calgary, AB
Canada

ISSN 2520-8284 ISSN 2520-8292 (electronic)
Hot Topics in Acute Care Surgery and Trauma
ISBN 978-3-030-92240-5 ISBN 978-3-030-92241-2 (eBook)
https://doi.org/10.1007/978-3-030-92241-2

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To those who do search, not just re-search.

Zsolt J. Balogh

To Tiana and Kyra and all the patients and families who have consented to clinical research to provide better care to future critically ill and injured strangers.

Andrew W. Kirkpatrick

To all severely ill patients who sought care and trusted their lives to us. Treating them was not a job or an obligation. It was a calling and a privilege.

Raul Coimbra

Series Foreword

Research is fundamentally altering the daily practice of acute care surgery (trauma, surgical critical care, and emergency general surgery) for the betterment of patients around the world. Management for many diseases and conditions is radically different than it was just a few years ago. For this reason, concise up-to-date information is required to inform busy clinicians. Therefore, since 2011 the World Society of Emergency Surgery (WSES), in partnership with the American Association for the Surgery of Trauma (AAST), endorses the development and publication of the "Hot Topics in Acute Care Surgery and Trauma," realizing the need to provide more educational tools for young in-training surgeons and for general physicians and other surgical specialists. These new forthcoming titles have been selected and prepared with this philosophy in mind. The books will cover the basics of pathophysiology and clinical management, framed with the reference that recent advances in the science of resuscitation, surgery, and critical care medicine have the potential to profoundly alter the epidemiology and subsequent outcomes of severe surgical illnesses and trauma.

Federico Coccolini
General, Emergency and Trauma Surgery Department
Pisa University Hospital
Pisa, Italy

Raul Coimbra
Riverside University Health System Medical Center
Riverside, CA, USA

Andrew W. Kirkpatrick
Department of Surgery and Critical Care Medicine
Foothills Medical Centre
Calgary, AB, Canada

Salomone Di Saverio
Department of Surgery
Madonna Del Soccorso Hospital
San Benedetto del Tronto, Italy

Foreword

This a timely review of the progress made worldwide over the past half century since the syndrome postinjury multiple organ failure (MOF) was first recognized. Trauma surgeons have been pioneers in this field. Edited by the authoritative professors Balogh and Coccolini, the list of chapter authors includes trauma experts who have defined and elucidated the underlying mechanisms of MOF. Collectively the careful documentation of data, hypothesis-driven research, and clinical application of findings have resulted in a marked reduction in mortality although the morbidity burden remains substantial. Appropriately the early chapters review the definition, varied terminology, and pathophysiology of MOF. Trauma surgeons were the first critical care providers to recognize the common signaling events resulting from infection-generated pathogen-activated molecular patterns (PAMPS) and shock/trauma-induced danger-activated molecular patterns (DAMPS). The next set of chapters covers the epidemiology and risk factors and adds the more recent perspective on the long-term consequences, i.e., the persistent inflammation, immunosuppression, and catabolic syndrome (PICS). These chapters lead into a discussion of management, emphasizing the importance of prompt reversal of shock and effective source control for secondary infections. The ensuing series of chapters discuss the organ-specific manifestations and their related supportive therapy. Importantly there is a chapter devoted to the demanding care of MOF in low-resource environments. The text concludes with a systematic review of randomized clinical trials that provide the basis for current therapeutic priorities and defining the remaining knowledge gaps that warrant further investigation. In sum, this is a comprehensive overview of the current management of postinjury MOF that will be invaluable for all health care providers managing the injured patient at risk for organ dysfunction.

Ernest E. Moore
Denver, CO, USA

Preface

Postinjury Multiple Organ Failure (MOF) is the ultimately feared complication among polytrauma patients who survive the initial insult of significant mechanical energy transfer to the body. It is common knowledge that it is the major contributor to late deaths after injury. It is extremely resource intensive on the health care system and society in general. In this *Preface*, we are sharing with you some less academic but more historical and anecdotal intricacies of the long affair that has been linked with MOF.

While polytrauma is a disease triggered by the impact of external energy on the organism, resulting in physiological derangements and systemic inflammatory response syndrome frequently leading to dysfunction of the uninjured organs, MOF is a syndrome not specific to trauma. Why postinjury MOF? Why trauma surgeons? The 50-year history of MOF started with observations and christening by trauma surgeons who can be traced back in PubMed or, more intriguingly, via multiple generations of mentor-mentee linages linking numerous institutions, countries, and continents. I am as young as MOF and already a third-generation explorer from the original Eiseman linage. I have never met Dr. Ben Eiseman, but I can very much relate with his mountaineering and outdoor-loving nature I learned from my immediate mentors Gene and Fred Moore from Denver during the 1990s.

Once you are intrigued by the mechanisms, pathophysiology, prediction, treatment, outcomes, and prevention of MOF, you are naturally studying traumatic shock, its resuscitation, the postinjury inflammatory response, the optimal timing of surgical interventions, and many aspects of postinjury critical care. MOF is an overarching pathological endpoint to avoid. Our North American trauma surgeon colleagues are historically in charge of their trauma ICUs, frequently double board-certified (surgery and critical care). Their system also offers trauma, acute care surgery, and critical care fellowships. In most other parts of the world, surgeons are involved in critical care on a consultative basis, and ICUs are staffed by nonsurgical critical care physicians staff open or increasingly closed ICUs. We believe trauma surgeons outside of North America need more involvement in the critical care of severely injured patients. Hopefully, this book will help simplify some principles of postinjury critical care, which are seemingly far too distant to many surgeons.

MOF was not recorded by ancient physicians of the Middle East, Egypt, Greece, or Rome. We needed more than 2000 years of medical advancements to

successfully treat single organ failures and keep critically ill patients alive until survival or subsequent organ failure. While a disastrous complication of polytrauma and other critical illnesses, MOF is also a measure of success for modern critical care. These advances have put the generation of Dr. Art Baue and many others in a situation where they had to face a condition they had never seen before, the progressive sequential failure of multiple organs. MOF in the 1970s looked like the complication of major penetrating abdominal trauma primarily driven by sepsis. But the syndrome from trauma aetiology has changed its face many times. During the 1980s, European trauma surgeons saw the problem frequently occurring from blunt polytrauma without any infection, driven primarily by acute lung injury and respiratory distress syndrome. These lead to a focus on ameliorating secondary lung injury via ventilatory strategies and gut-related interventions to minimise priming from the intestinal tract via bacterial and endogenous molecular motifs delivered to the lung by blood and lymph. While traumatic shock and some aspects of the resuscitation were always linked to MOF, the clear preventable association was identified by the late 1990s and early 2000s. The crystalloid-based haemodynamic goal-directed traumatic shock resuscitation coupled with the advancement of damage control surgery led to the early survival of many critically ill patients presenting in shock constituting a new challenging form of early MOF on the ICUs. These generally fluid overloaded patients were difficult to ventilate, had increased compartment pressures in several body compartments, and frequently continued to need additional transfusions and unplanned operations due to coagulopathy. Despite their optimised cardiac function and supranormal intravascular volume status, these patients developed hyperacute renal failure due to increased abdominal pressure without abdominal injuries, which would soon compromise cardiac filling and increased airway pressures to complete the picture of MOF due to abdominal compartment syndrome. Addressing abdominal compartment syndrome with coagulation-based haemostatic resuscitation strategies limiting crystalloid use in the treatment of traumatic shock virtually eliminated this form of early MOF. More recently MOF has been "tamed" from the raging syndrome of the young hyperinflamed young male to the less spectacular but equally lethal subclinical and more prolonged organ dysfunction of the frequently less severely injured elderly and with a more balanced sex distribution. Ever since the early 1970s, MOF has repeatedly challenged us. As soon as we solved a problem (abdominal sepsis, lung protective ventilation, haemostatic resuscitation) and outcomes started to improve, a new phenomenon emerged due to the survival of patients from injuries, which previously was never the case. Every month I see at least a couple of patients who would not have survived past day one a few years ago and I need to tell the family that we are experiencing something, which is not in the textbooks, not in scientific papers, we apply principles, anticipate what we can and manage proactively that what we know about MOF always brings something new and unexpected, and we are starting to see new common patterns, which may explain why organs fail in polytrauma patients following polytrauma or major trauma. This is probably the reason why MOF has not disappeared. Some advances specific to trauma care and generally applicable to critically ill patients have led to a significant decrease in mortality and

although the full-blown syndrome seems to be less severe and less protracted, the overall incidence remained the same among the high-risk polytrauma patients.

This makes sense as we are treating a polytrauma population at least 20 years older on average with more comorbidities and associated obesity. In developed trauma systems, due to aggressive early haemorrhage control and balanced resuscitation the previously strong independent predictors of MOF such as shock and resuscitation parameters are no longer relevant as predictors of MOF. Although not as strongly, markers of tissue injury severity remain independent predictors of MOF. Age as a surrogate for comorbidities and general health remained a stronger predictor of organ dysfunction and failure. The fine details of the pathophysiology of postinjury MOF can be debated, but most experts agree that it is strongly linked to inflammation. Laboratory animals with known pro-inflammatory phenotype (rats, mice) are likely to develop MOF after a relevant experimental insult while hibernating mammal species with functional quantities of brown adipose tissue (e.g. artic ground squirrels) and birds with less "sparky" mitochondria are unlikely to develop it. Excessive white adipose tissue in humans associated with a heightened baseline inflammatory state and higher BMI are not surprisingly strongly associated with postinjury MOF.

Trauma surgeons not just first described and coined the term MOF but developed and validated scoring systems to define the syndrome and monitor its epidemiology and outcomes. Currently, many longitudinal prospective institutional postinjury MOF registries exist, which regularly provide important reports on the changing aspects of the condition. Numerous research laboratories explored many aspects of the syndrome worldwide and described the essential components of the pathophysiology of MOF. It is hard not to emphasise the importance of endogenous (intracellular) damage-associated molecular patterns (DAMPs) in the development of MOF following polytrauma. This mechanism provides an explanation on how major tissue injury in patients without shock or exposed to pathogens upon presentation can lead to severe inflammation and secondary organ damage. Many of the DAMPs have mitochondrial (ancient proteobacteria) origin, which put these essential organelles again into focus beyond cellular energetic function in relation to the mechanism and treatment of postinjury inflammatory complications such as MOF.

We believe that this book provides an evidence-based overview of the current understanding of postinjury MOF. It also raises several questions from the very basics to the most complex therapeutics, which we have to address in the future. Why do not we have a uniform definition and consensus on MOF scoring? Why do we have so little and not necessarily trauma-specific level-1 evidence related to its treatment? Why do decades of basic science work have not had more impact on our clinical practice? Why cannot we describe when and how to best nourish polytrauma patients? When is the best time to perform non-lifesaving surgery to restore mobility without making the inflammatory state worse? What really is a second hit? Is it real or just a myth? What is the role of the microbiome? Are we just the pet human of our bacteria?

This textbook is aimed for students, trainees, and specialists interested in the care of the injured patient. It surely can over or underwhelm some on the far ends of the

knowledge and experience spectrum but will provide a comprehensive overview with a pragmatic order of chapters. The chapters are written by world experts in the field, and they are stand-alone readings even without the context of the entire book. We have tried to minimise overlaps among sections for those who prefer the cover-to-cover approach.

This book is another example of the stellar collaboration between the publisher (Springer Nature) and two academic societies (American Association for the Surgery of Trauma and World Society of Emergency Surgery), which have already produced many successful textbooks on challenging topics of trauma and acute care surgery by experts in their fields.

On behalf of my co-editors Professors Coccolini, Coimbra, Di Saverio, and Kirkpatrick we hope this book will be a valuable contribution to the optimal management of severely ill polytrauma patients wherever you practice around the globe.

December 2021

Newcastle, NSW, Australia — Zsolt J. Balogh
Moreno Valley, CA, USA — Raul Coimbra
San Benedetto del Tronto, Italy — Salomone Di Saverio
Calgary, AB, Canada — Andrew W. Kirkpatrick
Pisa, Italy — Federico Coccolini

Contents

The Definition of Multiple Organ Failure

1

Hannah Black

1.1 Defining MOF

The definition of Multiple Organ Failure (MOF) has progressed from previously described all-or-none phenomenon to what is now understood as a continuous process of varying degrees of organ dysfunction that lead to overt organ failure. This change in how the MOF syndrome can be recognised leads to the development of multiple scoring systems that attempt to quantitate the degree of organ failure [1]. MOF has also been described as a disease of medical progress, as technological advances in critical care improve there is an associated increase in survival as patients develop complications of critical illness that were previously not seen [1].

Most MOF scores were developed during the 1980s and 1990s with more than 40 organ failure severity scoring systems being proposed. Despite this, to date there is no single scoring system that is accepted as the gold standard measure for MOF. This leads to great variance in reported incidence, duration, severity and mortality associated with the syndrome. Without a standardised score, epidemiological and outcome comparisons between studies, institutions and populations are impossible and complicate the evaluation of changes in treatment and patient management [2, 3]. Most MOF soring systems were originally developed as descriptive measures, but have subsequently been validated and used as outcome predictors with the intention of rapidly identifying patients at high risk of developing MOF [2, 4].

H. Black (✉)
John Hunter Hospital, New Lambton Heights, NSW, Australia

School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia
e-mail: hannah.black@uon.edu.au

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_1

1.1.1 Marshal Multiple Organ Dysfunction Score (MODS)

The Marshall MODS [5] was developed in 1995, originally designed for critically ill patients admitted to ICU, it was later validated for use in the trauma cohort. The authors utilised a literature review and surgical admissions records to design measures of organ dysfunction against mortality. It includes six organ systems: respiratory, renal hepatic, cardiac, coagulation and Central Nervous System (CNS). The authors decided on a composite measure, pressure-adjusted heart rate (PAR), for cardiac failure as they deemed no single variable met the criteria, but this requires calculation [2]. All six organ systems are scored zero to four using the first measurement of the day and then added together to give a score of zero to 24 [6]. No MOF cut-off was originally given as the authors used the score to correlate with ICU and hospital mortality [5]. Studies which have validated the Marshall Score have defined MOF as a score of more than 5 for 1 day or two consecutive days [2, 6]. The Marshall score assesses organ dysfunction on the worst ICU day and assigns a maximum score to patients who do not survive [7].

1.1.2 Sequential Organ Failure Assessment (SOFA) Score

The SOFA Score [8] was developed in 1994 by clinicians and was initially used to describe critically ill ICU patients and predict mortality, but subsequently tested and validated for trauma patients [6]. The developers stressed that the organ system parameters needed to be simple, objective, easily and routinely measured in the ICU, able to be repeated, independent of therapeutic interventions and should be continuous measures [2]. The SOFA Score assesses the same six organ systems as the Marshall Score, but uses mean arterial pressure and a surrogate parameter, therapeutic interventions with vasopressors, therapy-dependent, to measure the cardiovascular system. The score is obtained by summing the worst daily value for each system [6]. No time frame or categorical cut-off point for MOF definition was proposed by the developers [8]. It is utilised as continuous descriptive measure as a way of monitoring patients over time [3]. General consensus in the literature is that a score of three or greater for one organ system is defined as failure of that organ. The definition of MOF using the SOFA score varies with failure of at least two single organ systems [6] or an overall score of greater than five [2] having been recommended. SOFA is calculated daily and is used as a descriptor of the severity of organ dysfunction [7].

1.1.3 Denver Score

The Denver Score [9] was developed in 1991 by trauma experts. It was originally designed to assess adult post-trauma organ failure in patients with an Injury Severity Score (ISS) of greater than 15 and survived more than 48 hours post-injury [2, 6]. While initially including eight organ systems, the Denver Score was revised in the

mid-1990s and reduced to four organ systems: respiratory, renal, hepatic and cardiac [9]. As with the other scoring systems, the Denver Score was initially developed to describe the critically ill pro-inflammatory or septic trauma patient, but has subsequently been validated to predict outcomes in trauma patients [3]. It is important to note that the Denver Score excludes the hematologic system and Central Nervous System (CNS) which implicates severe Traumatic Brain Injuries (TBIs). It also uses the surrogate cardiovascular measure of inotropic medication, the same as the Marshall Score [6]. Using the Denver Score MOF is defined as a total score of more than three at or beyond 48 h post-injury [3].

1.1.4 Brussels Score

The Brussels Score was developed in 1998 around the same time as the Marshall score and was similarly designed to apply an objective standardised approach to clinical trials in the ICU, especially those involving sepsis. The Brussels score examines the same six organ systems as the Marshall and SOFA scores: respiratory, renal hepatic, cardiac, coagulation and Central Nervous System (CNS) [7]. The Brussels score measures cardiovascular dysfunction/failure differently to SOFA and Marshall. Brussels measures hypotension and acidemia; however, acidemia can be caused by factors unrelated to the cardiovascular system, therefore does not necessarily reflect cardiovascular dysfunction or failure [8]. Unlike other MOF scoring systems, the Brussels score does not attempt to compound the severity of organ failure into a single score, marinating focus on the individual organ systems [7]. For patients who do not survive, the Brussels score calculates organ failure-free days [7].

1.1.5 Knaus Score

The Knaus score was originally designed in 1985 for its prognostic capabilities in order to quantify organ system failures and provide objective estimates of the probability of survival for ICU patients receiving intensive therapy [10]. The Knaus score is independently applied to each 24-hour period. It stipulates organ failure must be present on three consecutive days to exclude patients with transient organ dysfunction [1]. The Knaus score examines five organ systems: cardiovascular, respiratory, renal, haematology and neurologic [10]. Fry and Deitch subsequently added scores for hepatic and gastrointestinal dysfunction [1].

1.1.6 Goris Score

Goris et al. (1985) was one of the first attempts to quantify the severity of organ dysfunction and failure based on expert opinion in surgical intensive care patients. The only source of information for designing the score was clinical judgement and the experience of ICU experts. Seven organ systems were scored: respiratory,

cardiovascular, renal, hepatic, haematological, gastrointestinal and neurological. Organ dysfunction was scored one point, while organ failure was scored two points. The Goris score was validated in patients who required more than 3 days of ICU care and the maximum score was defined as the highest daily MOF score observed during the ICU stay [11].

1.1.7 Same Syndrome, Different Score

While all scores define the same syndrome, there are significant differences in which organ systems are selected, how they are assessed and at what time points MOF is measured. It is these differences that contribute to the variability of MOF incidence between studies and complicate comparison of studies.

Importantly, these scores were not originally developed to predict patient outcomes. As MOF is a major complication in severely injured trauma patients, the ability to score MOF is relevant both clinically, to identify at-risk patients, and in research, to determine what factors influence the development of MOF and to identify suitable patients for clinical trials. It is now recognised that MOF should only be defined at or after 48 hours post-injury as reversible physiologic derangements during the early post-injury period do not represent a substantial organ failure and are influenced by the traumatic injury itself. Therefore, today most studies concede that MOF score values are appropriate from day three [3, 6]. Vogel and colleagues have been investigating a scoring system for Emergency Department patients to predict MOF. The score has been shown more to accurately predict MOF than attending emergency physician estimations [12, 13]. Historically, the MODS and Denver Scores have been used for trauma research [2].

1.1.8 Evaluation of Scores

Each of the scoring systems have proved to be good predictors of MOF but have different specificities and sensitivities. SOFA is the most balanced between specificity and sensitivity [6]. Marshall is more sensitive reflecting a high incidence of MOF with low case-fatality rate. Denver score is more specific with low incidence of MOF and a high case-fatality rate [14]. Marshall and SOFA have consistently showed increased incidence when compared to Denver which may be related to their inclusion of the CNS as TBIs are associated with increased mortality in the trauma cohort [6]. It is sometimes very difficult to obtain head injury scores in the ICU trauma patient as they are often sedated or intubated for substantial periods of time. The Denver and SOFA score are good at predicting ICU resource use with SOFA performing slightly better. Denver and Marshall have been comparable for predicting mortality, ICU length of stay and ventilator days [3].

The Denver Score has low sensitivity, high specificity and therefore better prediction of adverse clinical outcomes and ICU resource utilisation [15]. Low sensitivity, however, can also result in missed “true-positive” cases of MOF [3]. The

Denver Score can also be used as a continuous scale to monitor response to treatment [15]. The high specificity of the Denver Score means that ICU resources can be better targeted to high-risk patients; however, it has the risk of missing potentially affected patients due to its low sensitivity [2]. Various studies who compared MOF scoring systems have recommended the use of the Denver Score for severely injured trauma patients as it accurately predicts adverse outcomes to high specificity, targeting a highly vulnerable and at-risk group of patients, and can be used as a continuous measure for monitoring response to treatment [2, 15]. It is also important to note that as the Denver score measures daily data after 48 h it is not influenced by reversible derangements due to incomplete resuscitation [16].

Summary of Most Commonly Used MOF Scores [6]

Dysfunction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Denver score					
Pulmonary, PaO2/FIO2, [mmHg]	>208	208–165	165–83	<83	
Hepatic, bilirubin, [μmol/L]	<34	34–68	69–137	>137	
Renal creatinine, [μmol/L]	<159	160–210	211–420	>420	
Cardiac inotropes[a]	No inotropes	Only 1 inotrope at a small dose	Any inotrope at moderate dose or > 1 agent at small dose	Any inotrope at large dose or > 2 agents at moderate dose	
SOFA score					
Pulmonary, PaO2/FIO2, [mmHg]	>400	≤400	≤300	≤200	≤100
Coagulation, platelet count, [×103/μL]	>150	≤150	≤100	≤50	≤20
Hepatic, bilirubin, [μmol/L]	≤20	20–32	33–101	102–204	>204
Cardiovascular, inotropes[b] in μg/kg/min	No hypotension	Mean arterial pressure < 70 mmHg	Dopa ≤5 or any Dobu dose	Dopa >5 or Epi ≤0.1 or Nor ≤−0.1	Dopa >15 or Epi >0.1 or Nor >0.1
Renal, creatinine, [μmol/L]	<110	110–170	171–299	300–440	>440
Central nervous system, GCS	15	13–14	10–12	6–9	<6
MODS					

Dysfunction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Pulmonary, PaO2/FIO2, [mmHg]	>300	226–300	151–225	76–150	≤51
Renal, creatinine, [μmol/L]	≤100	101–200	201–350	351–500	>500
Hepatic, bilirubin, [μmol/L]	≤20	21–60	61–120	121–240	>240
Cardiovascular, PAR[c]	≤10.0	10.1–15.0	15.1–20.0	20.1–30.0	>30.0
Coagulation, platelet count, ×103/μL	>120	81–120	51–80	21–50	≤20
Central nervous system, GCS	15	13–14	10–12	6–9	<6

[a] Inotrope doses (in μg/kg/min): vasopressin: small <0.03, moderate 0.03–0.07, large >0.07; dopamine: small <6, moderate 6–10, large >10; dobutamine: small <6, moderate 6–10, large >10; epinephrine: small <0.06, moderate 0.06–0.15, large >0.15; norepinephrine: small <0.11, moderate 0.11–0.5, large >0.5

[b] *Dopa* Dopamine, *Dobu* Dobutamine, *Epi* Epinephrine, *Nor* Norepinephrine

[c] PAR = Heart Rate × Central Venous Pressure/Mean Arterial Blood Pressure

References

1. Durham RM, Moran JJ, Mazuski JE, Shapiro MJ, Baue AE, Flint LM. Multiple Organ Failure in Trauma Patients. J Trauma Acute Care Surg. 2003;55(4):608–16.
2. Hutchings L, Watkinson P, Young JD, Willett K. Defining multiple organ failure after major trauma: a comparison of the Denver, sequential organ failure assessment, and Marshall scoring systems. J Trauma Acute Care Surg. 2017;82(3):534–41.
3. Dewar DC, White A, Attia J, Tarrant SM, King KL, Balogh ZJ. Comparison of postinjury multiple-organ failure scoring systems: Denver versus sequential organ failure assessment. J Trauma Acute Care Surg. 2014;77(4):624–9.
4. Dewar DC, Tarrant SM, King KL, Balogh ZJ. Changes in the epidemiology and prediction of multiple-organ failure after injury. J Trauma Acute Care Surg. 2013;74(3):774–9.
5. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med. 1995;23(10):1638–52.
6. Fröhlich M, Wafaisade A, Mansuri A, Koenen P, Probst C, Maegele M, et al. Which score should be used for posttraumatic multiple organ failure? - comparison of the MODS, Denver- and SOFA- scores. Scand J Trauma Resusc Emerg Med. 2016;24(1):130.
7. Bernard GR. Quantification of organ dysfunction: seeking standardization. Crit Care Med. 1998;26(11):1767–8.
8. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707–10.

9. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC. Postinjury multiple organ failure: a bimodal phenomenon. J Trauma Acute Care Surg. 1996;40(4):501–12.
10. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. Prognosis in acute organ-system failure. Ann Surg. 1985;202(6):685–93.
11. Goris RJ, te Boekhorst TP, Nuytinck JK, Gimbrère JS. Multiple-organ failure. Generalized autodestructive inflammation? Arch Surg. 1985;120(10):1109–15.
12. Vogel JA, Newgard CD, Holmes JF, Diercks DB, Arens AM, Boatright DH, et al. Validation of the Denver emergency department trauma organ failure score to predict post-injury multiple organ failure. J Am Coll Surg. 2016;222(1):73–82.
13. Vogel JA, Liao MM, Hopkins E, Seleno N, Byyny RL, Moore EE, et al. Prediction of postinjury multiple-organ failure in the emergency department: development of the Denver emergency department trauma organ failure score. J Trauma Acute Care Surg. 2014;76(1):140–5.
14. Sauaia A, Moore FA, Moore EE. Postinjury inflammation and organ dysfunction. Crit Care Clin. 2017;33(1):167–91.
15. Sauaia A, Moore EE, Johnson JL, Ciesla DJ, Biffl WL, Banerjee A. Validation of postinjury multiple organ failure scores. Shock. 2009;31(5):438–47.
16. Dewar D, Moore FA, Moore EE, Balogh Z. Postinjury multiple organ failure. Injury. 2009;40(9):912–8.

2 The Pathomechanism of Post-Injury Multiple Organ Dysfunction Syndrome (MODS)

Etrusca Brogi, Federico Coccolini, and Francesco Forfori

2.1 Introduction

In 1975 for the first time, Baue reported a new clinical syndrome described as "multiple, progressive or sequential systems failure" in trauma patients [1]. This syndrome was characterized by a similar pattern of progression over time, involving 2 or more organs, induced by different acute insults. Thereafter, several new definitions have been proposed. Nowadays, multiple organ dysfunction syndrome (MODS) is defined as a clinical syndrome characterized by the development of progressive and potentially reversible physiologic dysfunction in 2 or more organs or organ systems that can be triggered by a variety of acute insults, including sepsis, trauma, burns, pancreatitis and hypovolemic shock [2]. Regardless of the nature of the initial insults, MODS represents a common clinical final pathway characterized by a progressive functional failure of several organ systems due to an inappropriate uncontrolled systemic inflammatory response; this unbridled activation of the inflammatory response lead to a loss of the host's ability to localize the inflammation on the site of injury, resulting in a systemic inflammation, severe host tissue damage and subsequent MODS. The systemic inflammatory response syndrome (SIRS) is the clinical manifestation of systemic inflammation characterized by fever/ hypothermia, leucocytosis /leukopenia, tachycardia and tachypnoea [3].

Paradoxically, MODS represents the result of advancement in trauma and critical care management. In fact, the advances in organ-specific supportive treatment have decreased the mortality during the acute phase, possible leading to a post-injury

E. Brogi (✉)
Department of Anaesthesia and Intensive Care, Bufalini Hospital, Cesena, Italy

F. Coccolini
Department of Surgery, University of Pisa, Pisa, Italy

F. Forfori
Department of Anaesthesia and Intensive Care, University of Pisa, Pisa, Italy

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_2

multiple organ failure (MOF). MODS represents one of the major causes of morbidity and mortality in trauma and intensive care patients [4]. The reported incidence varies widely in literature, from 7 to 66%, due to the use of different scoring system and population included [5]. However, over the year, in literature are reported important changes in the epidemiology of MODS, with a significant decrease in MODS incidence, severity and mortality [6]. This changing epidemiology has been thought to be due to an improvement in early resuscitation, changes in resuscitation strategies (e.g. decreased use of blood products transfusion) and early goal-directed ICU therapies. Important advances in critical care, that have decreased the incidence and severity of MODS, are represented by recognition of abdominal compartment syndrome, lung protective ventilation, glycaemic control, early enteral nutrition, reduction on blood transfusion, damage control surgery, renal replacement therapy and cortisol replacement for adrenal insufficiency. Post-trauma MOF accounts from 51% to 61% of mortality with an increased ICU stay [3]. Even more, the incidence and mortality of MOF are influenced by the type of trauma; blunt (13%) versus penetrating (3%) trauma [7]. The mortality increases with the number of the affected organ; from 30% in the presence of single organ dysfunction to 76.2% in the case of 4 affected organs [8]. The respiratory tract was found to be the most common site involved in MOF and had the strongest association with mortality [8]. In patients with sepsis, the lung represents the most frequent site of infection followed by the abdomen. Mortality is also associated with pre-existing disease.

The understanding of MODS pathophysiology has progressively advanced over the time; while the main effectors and mediators (i.e. neutrophils, macrophages, endotoxin, cytokines and oxidants) have been identified, the disease processes responsible for the pathogenesis of MODS have still to be clarified deeply [9]. In fact, the mechanism and cellular pathophysiology involved in the transition from SIRS to MODS remain unclear. However a major role is played by the cross-talk between signalling pathways, the individual genetic polymorphisms (e.g. difference in constitutive expression and upregulation of mediators) and the activation of positive circulating loop through inflammatory mediators [10–13]. The “two-hit” hypothesis has recently been proposed in order to explain the development of MODs in trauma and critically ill patients [14]. In this model, a first severe insult (e.g. trauma, burn, infection) primes the host immune system resulting in a significant neutrophilia at 3 h post-injury [3]. The neutrophilia represent a vulnerable window when a subsequent second insult (“the second hit”) may induce an exaggerated unbridled host immune response, which can lead to multiple organ dysfunction syndrome and death. The intensity and severity of the inflammatory response are determined by host factors and the nature of the precipitating injury characteristics. However, the key element for the pathophysiology of MODS is represented by the loss of the equilibrium between the pro-inflammatory and anti-inflammatory response due to a dysregulated immune response. Furthermore, even if systemic inflammation is characterized by a common final pathway with the production of cytokines, mediators and the subsequent priming of polymorphonuclear cells (PMNs), the immune status may vary widely between organs [15]. This is due to the fact that transcriptional programmes, constitutive expression and upregulation of

inflammatory mediators differ in the singular organ [16]. The gene expression is specific to a particular organ, consequently, each organ presents specific mechanism of dysfunction during SIRS and MOF.

The clinical manifestation and severity of MODS are influenced by host factors (e.g. age, comorbidities, genetic predisposition) and the severity of the injury. Genetic predisposition is an important factor that has to be taken into account [17, 18]. Genetic polymorphisms are proven to play a role in the development of MOF. In fact, the genomic variance may affect the expression and the upregulation of inflammatory molecules, influencing the severity of MOF. Individual genomic and phenotype, consequently, gene expression and protein production capacity, is tightly linked to the susceptibility to complications after an injury and influences the likelihood to develop MODS. The dosage of these molecules can potentially be used as biomarkers to diagnose and determine the prognosis [12]. Furthermore, the understanding of the important role of genetic polymorphism has resulted in the development of novel therapeutic strategies to prevent or treat MODS, with contrasting results. Cytokines target therapy, antagonist targeting adhesion molecules, antioxidants and treatment strategies to remove excessive cytokines and toxins (e.g. CytoSorb®, Toraymyxin) can represent possible therapeutic options for the prevention and the treatment of MODS [19, 20]. However, we have to take into account that MODS is characterized by a positive and redundant positive feedback though inflammatory mediators, consequently, target therapy on a single pathway is not sufficient to improve outcome.

2.2 Pathophysiology

The initial immune response to an insult is provided by the innate component of the immunity system. Innate immunity represents the first line of defence/first response system of the host towards a warming signal and is able to respond quickly to a wide range of stimuli. The main function of this component of immunity is to fight and contain infection at the entrance door, giving time to the antigen-specific immune system to develop an effective response. The activation of innate immunity cells is activated by threatening signals, which can come from internal sources (e.g. tissue damage, cell lysis components), or from external agents (e.g. surface or genetic molecules of microorganisms). The fact that the answer can be activated both by internal and external signs explains the common final molecular pathway that can be triggered both by infectious pathogens and non-infectious causes (i.e. trauma, burns and pancreatitis) [21]. A central role is played by pattern recognition receptors (PRRs), capable of recognizing pathogen-associated molecular patterns (PAMPs) and danger-associated molecular pattern molecules (DAMPs). The interaction between pathogen-specific proteins and the host proteins leads to the trigger of intracellular signalling cascades and the release of pro-inflammatory cytokines [22]. This represents the first line of defences against invading pathogens.

The effector cells of innate immunity are cells of the monocyte-macrophage line, Natural Killer (NK), endothelial cells and dendritic cells. These cells, activated by

pathogens, secrete mediators of inflammation, including cytokines (e.g. TNF-α, IL-1 and IL-6), chemokines (e.g. IL-8), prostaglandins and histamine [21]. These mediators act at the level of the endothelium causing vasodilation, an increase of vascular permeability and tissue recruitment of neutrophils. Furthermore, the procoagulant state often observed during chronic inflammatory response is due to a crosstalk between inflammation and coagulation. In fact, inflammatory response leads to an upregulation of endothelial tissue factor, a reduction of circulating level of protein C, antithrombin III, thrombomodulin and an enhancement of inhibitors of fibrinolysis; with consequent enhancement of the coagulation cascade [23].

2.2.1 PAMPs, DAMPs and PPRs

Receptors for PAMPs and DAMPs are called pathogen recognition receptors (PPRs) expressed either from cells of the immune system and from the cells of epithelial barriers, that allow the host to recognize the pathogen and to initiate the innate immune response [24]. The PPRs are mainly represented by the Toll-like receptors (TLRs) family, transmembrane receptors expressed by different cell types: leukocytes, cells of the monocyte-macrophage line, Natural Killer, dendritic cells, endothelial cells and fibroblasts [24]. The NLR (nucleotide-binding domain leucine-rich repeat containing) are a family of intracellular PPRs with the function of regulators of the innate immune response against microbial pathogens [25]. Following the binding of PAMPs with TLRs (or with the NLRs) an intracellular signal transduction cascade is activated, mediated by different kinases. The final event of this transduction cascade is the activation of a transcriptional programme, which includes the nuclear transcription factor NF-kB, the mediator of the expression of genes that code for inflammation factors, such as cytokines, chemokines and nitric oxide [24]. Consequently, the common final response to an insult is the release of proinflammatory cytokines.

Toll-like receptors family are expressed by different cell type including the airway the gut epithelial cells, haematopoietic cells, mast cells, regulatory T lymphocytes, endothelial cells and NK cells. A total of 10 different TLRs have been identified; TLR2 interacts with components of Gram-positive bacteria (i.e. peptidoglycans and lipoproteins), viruses and fungi [24]. Some TLRs are able to respond to microbial ligands independently, but in some cases they require the presence of other molecules present on the cell surface (e.g. CD14, MD2) to facilitate the binding between PAMPs e TLR. As an example, TLR4 is the first TLR documented with a role in pathogen recognition, which identifies and interact with LPS of gram-negative bacteria. TLR4 forms a complex with LPS through the aids of CD14 and LPS binding protein. The complex then recruits Toll-IL1 receptors domain, the TIR domain-containing adaptor molecules (TRIF) and myeloid differentiation factor 88 (MyD88) leading to the activation of NF-κB and the subsequent production and release of TNF-α, IL-1 and IL-6 [24, 26]. Some TLRs, such as TLR4 and TLR2, are located at the level of the cytoplasmic membrane and recognize wall components of microbial cell; others, such as TLR3 and TLR9, are found at the endosomal level

and are responsible for binding components of phagocytized microorganisms (for example TLR3 is responsible for recognition of viral dsRNAs) [27] [28]. However, many microorganisms present more than one TLR ligand and it is likely that microorganisms with different molecular patterns can cause differential activation of numerous TLRs, thus allowing different answers to different classes of pathogens. Since the activation of TLRs can trigger a rapid and powerful inflammatory response, it must not surprise that the signal of the TLRs is subjected to regulation at various levels. Some of the regulatory molecules are constitutively expressed at the level of tissues and plasma, while others are induced by the activation of the TLRs path and therefore involve a negative feedback.

PAMPs (Pathogen-associated molecular patterns) are the components of the microorganisms that activate the immune response [29]. Lipopolysaccharide (LPS), the main component of the wall of Gram-negative bacteria, is one of the major triggers of the septic signalling cascade. Other examples of PAMPs are represented by the peptidoglycan (a main component of the Gram-positive wall), mannose-rich glycans, bacterial flagellin, lipoteichoic acid, hyaluronidase and nucleic acid (e.g. bacterial DNA, double-stranded or single-stranded RNA). On the other hand, danger-associated molecular pattern molecules (DAMPs), also known as damage-associated molecular pattern molecules or alarmin, are host molecules capable of initiate a non-infectious inflammatory response [30, 31]. DAMPs include nuclear or cytosolic proteins released from the cell or exposed on its surface following tissue injury. Examples of DAMPs are heat-shock proteins, HMGB1, hyaluronan fragments, ATP, uric acid, heparin sulphate, S100 protein and DNA. In fact, trauma can activate the innate immune system through DAMPs. High-mobility group box 1 (HMGB1) is released by necrotic cells and acts as pro-inflammatory mediators activating macrophages [32]. HMGB1 may stimulate the maturation of dendritic cell through the upregulation of CD80, CD83, CD86 and CD11c, can promote the production of IL-1, TNF-a, IL-6, IL-8 in myeloid cells and can increase the expression of cell adhesion molecules (ICAM-1, VCAM-1) on endothelial cells. It has been demonstrating that high levels of HMGB1 are associated with epithelial and gut barrier dysfunction and has recently been implicated as a key molecular pathway in trauma/haemorrhagic shock. HMGB1 interact with TLR2, TLR4 and RAGE receptors.

DNA and RNA, released after cell necrosis, can act as DAMPs too. DNA can trigger the inflammatory responses through the TLR9 receptors and DAI, whereas, RNA activates TLR3. Even more, injured tissue release protease that degrades proteoglycans, leading to the liberation of heparin sulphate (HS); an endogenous TLR4 agonist [33].

2.2.2 Two-Hit Model

Once the immune response is triggered, the production and release of cytokines (i.e. TNF-α, HMGB1, IL-1) and chemical factors (i.e. IL-8, histamine, bradykinin, serotonin, leukotrienes and prostaglandins) from immune cells cause local

vasodilatation and the migration of immune cells to the sites of infection. Even more these cytokines are responsible for the enhancement of adhesion molecules on neutrophils (e.g. L-selectin and CD11/CD18) and endothelial cells (e.g. E, P-selectin and ICAM-1) leading to a tight bond and subsequent migration of neutrophils through the endothelium into the injured tissue where these cells produce and release reactive oxygen species (ROS) and protease. The release of these mediators triggers an acute inflammatory response and endothelial damage with increased permeability, swelling and necrosis. In fact, endothelial cell dysfunction is a common pathophysiological characteristic in MOF syndrome and it is considered as a precursor of tissue damage and organ failure [34]. Pro-inflammatory cytokines play a central role in initiating, amplifying and perpetuate an inflammatory response. TNF-α, IL-1 β are the major pro-inflammatory mediator in the acute-phase response. Besides TNF-α and IL-1 β, Il-6 regulate the generation of C-reactive protein, procalcitonin, serum amyloid A and complement factors [35]. Even more, IL-6 regulates the growth and differentiation of lymphocytes and activates NK and neutrophils.

The complement system can be activated during this immediate host defence response through the three initial pathways of activation: the classical, the lectin and the alternative pathways [36]. The effects of complement activation is represented by the production of biologically active peptides (C3a, C3b, C4b, C5a, C5b). C5b presents many functions; chemotaxis of leucocytes, degranulation of phagocytic cells, mast cell and basophiles, increase of vascular permeability, induce the expression of P-selectin in endothelial cells [37]. Even more, the active peptides of complement may activate the coagulation cascade by inducing expression of tissue factors [38]. In fact, the stimulation of coagulation, the downregulation of anticoagulant pathways and the impairment of fibrinolysis play a crucial role in this acute phase [38].

The activation of coagulation and the consequent fibrin deposition represent a great contribution to the host defence against microbial dissemination, reducing bacterial capacity to disseminate into nearby tissues and systemic circulation; leading to a compartmentalization of bacteria and reduces bacterial invasion. The coagulation cascade can be activated both by the expression of tissue factor (TF) by injured tissue or induced by pathogen-associated molecular patters, on monocytes and macrophages. Furthermore, TNF-α increase the production of platelet activating factor (PAF) with a consequent increase in procoagulant activity. Consequently, the procoagulant state observed during inflammatory response is due to a cross-talk between inflammation and coagulation [39]. The inflammation and coagulation interact and amplify the pro-inflammatory response, leading to a worsening of endothelial dysfunction [40]. However, physiologically, this procoagulant reaction is quickly inhibited by an increased synthesis of plasminogen activator inhibitor-1 (PAI-1) and reversed by activation of fibrinolysis [23]. The loss of this haemostatic system may lead to the excessive activation of coagulation, the downregulation of anticoagulant pathways and the impairment of fibrinolysis resulting in microvascular thrombosis and hypoperfusion. Thus, the dysregulation of the haemostatic system may lead to disseminated intravascular coagulation (DIC) [41].

Physiologically, all the abovementioned mechanisms are modulated by down-regulatory systems. The balance between pro and anti-inflammatory cytokines productions allows the maintenance of the homeostasis. IL-10 is one on the mainly implied anti-inflammatory cytokines in this phase and inhibits the production of TNF-α, IL-6 and IL-8 by monocytes and macrophages. However, when this equilibrium is lost, the resultant predominance of pro-inflammatory state leads to a systemic inflammatory response syndrome (SIRS) and eventually to MOF. On the contrary, the prevalence of anti-inflammatory state leads to immunoparalysis.

Tissue damage or the invading pathogens initiating the inflammatory response represents the first hit of the "two-hit hypothesis" of MOF. As already explained, polymorphonuclear cells (PMNs), monocytes and macrophages play a central role in the immune response after injury. The mobilization of PMNs results in neutrophilia, consequent inflammation and organ damage; this represents a vulnerability window during which a second hit can lead to MOF [42]. A variety of nosocomial and iatrogenic factors can act as a second hit and can be responsible for an excessive and dysregulated inflammatory response leading to MOF (e.g. mechanical ventilation, transfusion, abdominal compartment syndrome, ischemia/reperfusion syndrome and "gut" hypothesis).

- Ventilator-induced lung injury (VILI) is an acute lung injury that develops during positive mechanical ventilation mainly due to overdistension of alveoli and cyclic atelectasis [43]. The application of excessive volume during ventilation leads to severe injury of the alveoli and the consequent production of pro-inflammatory cytokines and reduction of surfactant production, thus decreasing lung compliance [44]. Even more, the damage of the endothelial barriers results in the migration of the pro-inflammatory cytokines systemically [45]. The loss of pulmonary compartmentalization allows these mediators to active an inflammation response on distant organs with the potential development of MOF. Consequently, VILI not only can aggravate ongoing lung injury but also it may have important systemic consequences (e.g. increased intestinal permeability, cellular apoptosis, immunosuppression). It can explain the tight association between acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF). In fact, VILI can represent a "second hit" exacerbating the pulmonary and subsequently trigger a systemic inflammatory response.
- Blood products contain mediators that may act as immune modulators. Blood transfusions are associated with an increased rate of SIRS, increased risk of developing MOF and increased mortality. Blood transfusion is considered one of the major predictors of developing MOF after trauma (as shown in Table 2.1) [3]. Many studies have shown that the transfusion of more than 6 red cell concentrate units in the first hours represent an independent risk factor for the development of MOF. Even more, the age of the blood products represents an independent risk factor for MOF [46]. Platelet, fresh frozen plasma and coagulation factors are also immunoactive and may play as a second hit [47].
- Ischemia/reperfusion injury occurs in a variety of clinical setting such as trauma, haemorrhagic shock, cardiac arrest and compartment syndrome. It is

Table 2.1 Independent risk factor for MOF

Predictor of severe MOF
Age > 55
Male gender
NISS, ISS > 25
Units of RBC transfusion>6 within 12 h
Base deficit >8 mEq/L in 0–12 h
Lactate levels>2.5 at 12–24 h
Thrombocytopenia
Age of transfused blood
Obesity
Abdominal compartment syndrome
Traumatic brain injury

MO multiple organ failure, *NISS* New Injury Severity Score, *ISS* Injury Severity Score, *RBC* red blood cells

characterized by two phases; a period of ischemia and temporary deprivation of tissue nutrients and oxygen followed by the reperfusion stage. The lack of blood supply leads to a switch from aerobic to anaerobic cellular metabolism. During the first phase, the hypoxemia is responsible for a decrease in ATP production and the degradation of ATP to ADP and subsequently to inosine and hypoxanthine [5]. The consumption of ATP is responsible for the loss of several cell functions: alteration of sodium/potassium pump, increase of intracellular Na+, cellular swelling and disruption of cellular integrity, alteration in cytosolic Ca + 2 concentration and activation of phospholipase and protease resulting in cellular damage. During the reperfusion phase, oxygen reacts with hypoxanthine, accumulating in the tissue during the ischemic state, through xanthine oxidase, resulting in the production of superoxide anion. Superoxide anions are further reduced to hydrogen peroxide and to hydroxyl ions [9]. These free radicals oxidant products cause the peroxidation of the cellular membrane leading to cellular necrosis. Even more, they can play a role as inflammatory mediators perpetuating and amplifying the systemic inflammatory response and leading to MOF. Haemorrhagic shock following trauma cause body hypoperfusion followed by subsequent reperfusion during resuscitation. Reperfusion of ischemic gut cause release of cytokines, pro-inflammatory lipids and proteins from the splanchnic bed. These mediators are then transported via mesenteric lymph to vascular circulation, especially the lung, where they prime PMNs (as explained below).

– The role of the gut: the alteration in the structure and permeability of the intestinal mucosa represent a source of bacterial products and inflammatory mediators that penetrate the systemic circulation and damage remote organ [5]. The disruption of tight junction and the decrease in mucosal perfusion due to ROS and inflammatory cytokines allow the migration of commensal bacteria and cytokines itself into the blood stream [48]. In fact, the gut is capable of producing IL-6 and TNF following an insult [9]. Even more, gut-associated lymphoid tissue (GALT) has the duty of maintaining mucosal immunity, producing IgA by

B-lymphocytes. IgA is responsible for balancing the release of TNF and IL-6 and to inhibit the neutrophils priming [49]. Furthermore, IgA can trap the pathogens and allows their expulsion. Important cross-talk occurs between intestinal epithelium, mucosal immune system and intestinal bacteria. During ICU stay, several factors can play a crucial role promoting bacteria overgrowing and breakdown of mucosal integrity; the limitation of enteral feeding promotes bacteria overgrowing and breakdown of mucosal integrity, dysbiosis due to use of broad-spectrum antibiotics, hypoperfusion due to amine usage, ischemia/reperfusion injury after resuscitation. A reduction of IgA production can be due by nutritional deprivation and after ischemia/reperfusion injury [50]. The fall in IgA levels predisposes to infectious complications. Even more, it has been recently observed that gut dysfunction may promote lung injury and hepatic dysfunction through the migration of gut–derived inflammatory mediators via mesenteric lymph and portal circulation. In the light of these evidences, gut and mesenteric lymphatic can be considered as pro-inflammatory organs. Intestinal phospholipase A2 (PLA2) generates arachnoid acid and 5-lipoxygenase products that act as pro-inflammatory mediators and are thought to be the responsible mediators that link splanchnic/gut ischemia/reperfusion injury to distant organ dysfunction [51].

2.3 Organ-Specific Mechanism of Dysfunction

2.3.1 Lung

The lung presents a central role during MOF and it is often the first organ to undergo dysfunction. Acute respiratory distress syndrome (ARDS) serious worsens patients' outcome, with associated mortality rate rising to 60% [22]. Regardless of the nature of the first insult, that can be either direct (e.g. pneumonia, ventilator-associated pneumonia, toxic aspiration) or indirect (e.g. pancreatitis, peritonitis, ischemia/reperfusion injury), the resident alveolar macrophages are activated. The subsequent production and release of pro-inflammatory mediators (cytokines, complement, prostaglandins, thromboxane) promote the migration and priming of neutrophils in the pulmonary vasculature [52]. PMNs produces various cytokines, ROS and protein kinases that perpetuate the influx of other PMNs leading to direct injury to the lung tissue, alteration of the endothelial and epithelial barrier and consequent oedema and cytokines influx to the bloodstream [53, 54]. Histological studies in the early phase of lung inflammation showed a marked accumulation of neutrophils in pulmonary oedema and in bronchoalveolar lavage (BAL). Even more, the injury of type II cells reduces the production of surfactant with alteration in normal lung compliance. Another important consequence of inflammation is represented by the activation of fibroblasts that are involved in injury repair processes with consequent formation of hyaline membranes and fibrin deposition. All these alterations are responsible for impaired in gas exchange and the subsequent necessity of mechanical ventilation. As abovementioned explained, mechanical ventilation itself can act as a "second hit" for the development of MODS [44].

TLR-4 and several cytokines play a crucial role in the pathogenesis of ARDS. Polymorphic variations of TLR-4 and the consequent amount of NF-kB activity can predispose patients to Gram-negative septic shock, with fewer ventilator-free days and increased mortality [55, 56]. Furthermore, genetic variation of TNF-α and TNF receptor increase the amount of circulation TNF and consequent worsening in outcome [56]. One promising target therapy currently under study is represented by anti-TNF antibody in patients with ARDS [57]. Other cytokines and mediators implied during the pathogenesis of ARDS are IL-1, IL-6, IL-8, IL-10, granulocyte colony stimulating factor (G-CSF), ICAM-1 and C5a [58, 59]. In the context of ARDS, another important protein that plays a crucial role is represented by the receptor for advanced glycation end-products (RAGE). This receptor is highly expressed in the lung and increased level of soluble RAGE (sRAGE) has been found in BAL of patients with ARDS [60]. The level of sRAGE correlates also with severity and mortality in such patient. RAGE can be activated by S100 proteins and advanced glycation end-products (DAMPs), leading to intracellular signalling cascades through NF-kB, mitogen-activated protein kinases (MAPK) and phosphoinositide 3-kinases (PI3K) and subsequent production and release of cytokines and ROS [61]. Inhibition of RAGE and its ligand (HMGB1) has been shown to decrease lung injury and improved survival [32]. Furthermore, the pharmacological blockage of the kinase activity of PI3K γ has shown to decrease neutrophil invasion and improve survival.

Apoptosis occurs through mitochondrial signalling and the activation of cell surface death receptors (Fas). In ARDS, high levels of Fas and its ligand (FasL) is observed in BAL and their levels are correlated with mortality [62]. Silencing the expression of Fas or Fas-associated death domain (FADD) decrease lung apoptosis, injury and inflammation during ARDS [63]. Finally, decreased levels of protein C are observed in ARDS (both septic and non-septic origin) and it correlates with poor outcome. Activated protein C (APC) play a central role not only for its anti-coagulation effects but also for several cytoprotective effects (e.g. decreasing apoptosis, reducing tissue factor and thrombin, the blockage of NF-kB). The treatment with human recombinant APC (rhAPC) has demonstrated significant reduction of mortality in patients with ARDS [64].

2.3.2 Myocardial Depression and Haemodynamic Changes

Myocardial depression is a frequent complication in septic patients. It can also occur in 50% of severe sepsis and septic shock and is responsible for the increased morbidity and mortality of these patients [65]. Sepsis-induced heart disease is a "global systolic and/or diastolic dysfunction". Even if the left ventricle is more sensitive to the negative effects of inflammatory mediators than the right ventricle, myocardial impairment can affect the left and/or right heart chambers [66]. The clinical manifestations of septic myocardiopathy are numerous and there are several pathogenesis mechanisms identified or hypothesized. Traditionally, it was thought that a myocardial depression was present only in the so-called "cold" or

hypodynamic phase of septic shock, however, it may occur also in the hyperdynamic phase; although masked by the observation of high values of range cardiac and reduced systemic resistance [67]. Both the direct effects of sepsis on the heart and the cardiac response to the hemodynamic modifications consequent to sepsis (e.g. variations in preloading, afterload and contractility, due to aggressive early treatment with fluids and vasoactive drugs) are implied in the pathogenesis of myocardial depression.

Myocardial depression represents the result of the complex interaction and synergism between mediators of the inflammatory response, metabolic modifications, mitochondrial dysfunction, adrenergic mediators, alterations of ion channels, alterations of autonomic autoregulation, anomalies structural, genetic factors, ischemic alterations, hemodynamic and microcirculation changes. Alterations in vascular endothelial, smooth muscle cells and cardiomyocyte function are central in the development of myocardial depression. During SIRS, several inflammatory mediators can show myocardial depressive effects. A fundamental role is played by the TNF-α, IL-1 and IL-6 [66, 68]. In fact, some clinical trials have shown that the infusion of monoclonal anti-TNF-α presents a significant increase in ventricular function in patients with septic shock [69]. However, the administration of anti-TNF-α monoclonal antibodies does not seem able to determine an improvement in survival [70]. Even if the mechanisms remain unclear, it is speculated that TNF-α and IL-1 are responsible for alterations in calcium function and for the production of nitric oxide (NO) [68]. Even more, serum levels of IL-6 are inversely related to the inotropism, probably through protein-kinases pathway [71].

Calcium channel changes result in a reduction of intracellular calcium with consequent impairment of the function of the contractile apparatus, with a shortening of the repolarization time of cardiomyocytes, consequent to a reduced L-type calcium channels activity [72]. Not only a direct effect of cytokines but also structural myocytes alterations may be responsible for reduction of myocyte contractility. In fact, post-mortem examinations showed the presence of myocardial infiltrates, mainly PMN cells, macrophages and monocytes. Inflammatory cells and fibrin as well were also observed in myocardial blood vessels.

NO presents direct and indirect negative effect on the heart [68]. In fact, the direct negative effects of NO are due to the intra-mitochondrial overproduction of peroxynitrite, lipid oxidation and myocyte glutathione depletion. Furthermore, NO induce vasodilatation, consequently, it effects on hemodynamics and on the myocardium can be remarkable. Some trials have shown an improvement in cardiac function after the use of iNOS [68]. Even more, it was found that the genetic pattern characterized by the absence of iNOS confers a certain resistance to the development of sepsis. The increased production of ROS can promote the self-amplification of the inflammatory response and increase the mitochondrial and myocardial contractile dysfunction. Consequently, in this context, the treatment with antioxidant substances could be reasonable to prevent or counteract the damage of ROS-induced organ of the septic patient.

Furthermore, cross-talk also exists between the central nervous system and the immune response. Activation of the sympathetic nervous system lead to an increase

of circulating epinephrine and norepinephrine, that bind the adrenergic receptors on macrophages that in turn release inflammatory mediators. Parallel, the cholinergic pathway is activated with the aim to act as an anti-inflammatory mediator. This leads to a resistance to the effect of catecholamine, a reduction of density of myocardial adrenergic receptors, an alteration of signal transduction and inhibition of protein expression G [73, 74]. Consequently, myocardial depression in the septic patient could be linked to the reduced response to endogenous and exogenous catecholamine.

Haemodynamic changes can also favour the development of myocardial dysfunction during sepsis. The main hemodynamic alterations in sepsis concern the reduction of intravascular volume, of vascular tone and the redistribution of flow between organs [74, 75]. Each of these factors can contribute differently to the severity of myocardial dysfunction. Hypovolemia may be absolute (due to increased losses, fluid shifts in the intracellular space due to increased microvascular and cellular permeability) and/or relative (due to the reduction of vascular tone and to the increased venous capacitance). Many mediators are responsible for hypovolemia in the septic patient, including endotoxins, cytokines, nitric oxide and peroxynitrite. Furthermore, the structural alterations of the glycocalyx can act synergistically to these factors in favouring vascular and cellular permeability. The consequences of hypovolemia, are the inadequate cardiac output and the redistribution of regional blood flow, at the expense in particular of the splanchnic and renal flow [76].

The reduction of vascular tone is mainly determined by the reduction of systemic vascular resistance following the imbalance between vasoconstrictor and vasodilator substances that coexist in the septic patient. Furthermore, reduced vascular response to the vasoconstrictor substances (e.g. catecholamines, angiotensin) is observed during sepsis due to "downregulation" of alpha-1 receptors (as already explained) [77]. Vasopressin levels can also be reduced in the septic patient, with a downregulation in the expression of receptors of vasopressin V1 [78]. Even more, the release of vasoactive inflammatory mediators (e.g. TNF-α, histamine, quinines, prostaglandins and prostacyclin, nitric oxide, peroxynitrite) leads to a further reduction of vascular tone. Since the ejection fraction (FE) is influenced not only by contractility but also by preload and afterload, the aforementioned changes in septic shock may explain why the FE does not always quantify and fully expresses the myocardial performance in a patient with septic shock.

2.3.3 Liver

The liver plays a relevant role in host defence; the reticuloendothelial system of the liver acts as a first line of defence in clearing bacteria and inflammatory mediators. However, the liver can represent a potential target of the inflammatory mediators. Even if liver dysfunction is traditionally viewed as a late event in multi organ failure syndrome, recent studies have revealed that liver dysfunction represents an early and prominent event in sepsis [79]. The major cells involved in the pathogenesis of liver dysfunction include Kupffer cells, hepatocytes and liver sinusoidal endothelial

cells [80, 81]. Furthermore, circulating priming neutrophils can also contribute to acute liver dysfunction, due to their production of inflammatory mediators and ROS.

Kupffer cells are specialized macrophages located in the liver, lining the walls of the sinusoids. These cells represent the first line defence against portal bacteraemia and endotoxemia; preventing microbial pathogens from entering into the systemic circulation. Even more, Kupffer cell is capable of producing inflammatory mediators within the lumen of the liver sinusoids, consequently, into the bloodstream with possible systemic dysfunction (e.g. lung dysfunction). The gut-derived catecholamine plays a vital role in the pathogenesis of liver dysfunction too. Gut-derived Norepinephrine binds adrenoceptors on Kupffer cells and consequently, the activation of Kupffer cells leads to release inflammatory mediators [82]. TNF-α, IL-1β, IL-6, IL-18, ROS and NO are produced and released by Kupffer cells with subsequent endothelial cell and hepatocyte injury. In particular, TNF-α plays a predominant role in the pathogenesis of liver failure. High level of TNF-α and their induced acute-phase protein (APPs) have been associated with the development of liver failure [83]. APPs enhance the procoagulant activity of endothelial cells, which can decrease perfusion. Even more, TNF-α can upregulate the expression of adhesion molecules, thus increasing the recruitment of priming neutrophils. TNF-α can directly stimulate hepatocytes to induce IL-6 production, increases the activity of cysteinyl aspartate-specific protease (caspase-3) and can activate mitogen-activated protein kinase (MAPK) [84]. All of these factors can contribute to the development of liver injury. As a consequence, excessive inflammatory mediators can induce endothelial damage, increased permeability and increased intra-hepatic resistance [85]. Even more, the inflammatory cascade can worsen the alteration of hepatic perfusion. Dysfunction of the endothelial cell barrier in combination with leukocytes and platelets recruitment in the liver microvasculature leads to the formation of microthrombi thus worsening liver tissue ischemia. At the same time, the production of NO is responsible for vasodilatation and consequent redistribution of blood flow, thus contributing to microvascular dysfunction [86].

Hepatocytes are responsible for regulating several metabolic pathways (i.e. glycogenolysis, gluconeogenesis, amino acid uptake), synthetizing coagulant factors, complement factors and acute-phase proteins. Hepatocellular damage can be a consequence of direct or indirect cytotoxic effects on hepatocytes and are responsible for several important systemic alterations. These changes include hyperglycemia, hyperlactatemia and protein catabolism. Hyperglycemia represents a consequence in increased hepatic glucose production and peripheral insulin resistance. Uncontrolled hyperglycemia is linked to increasing mortality and morbidity. Even more, during MOF, it is also possible to observe a hypoglycemic state due to depressed glucose production in chronic liver disease. Furthermore, hepatocyte dysfunction can have a deleterious consequence on coagulation cascade [85]. During MOF, the synthesis of protein C is significantly decreased and its level is correlated with the severity of the disease. Protein C is produced by the liver; activated protein C (APC) degrades Factors Va and VIIIa, thus preventing excessive thrombin formation. Alteration of hepatocyte function contributes to enhancing a procoagulant state during sepsis.

Finally, sinusoidal endothelial cells present also important immunoregulatory properties. In fact, these endothelial cells present the capacity of producing pro-inflammatory cytokines (e.g. NO, IL-1 and IL-6) and present the function of antigen-presenting cells for $CD4^+$ T cells [87]. Consequently, also endothelial cells present an important role in contributing to the development of liver dysfunction.

2.3.4 Kidney Failure

Acute kidney injury (AKI) is independently associated with increased mortality in critically ill patients. The mechanisms of AKI during SIRS and MOF remain unclear. However, AKI present deleterious systemic effects including damage to distant organs, consequently, AKI represents an important risk factor for the development and perpetuating of MODS. The major cells involved in the pathogenesis of kidney dysfunction include tubular epithelium, podocytes, endothelium and mesangial cells.

Even if kidney dysfunction is traditionally considered due to impairment in renal perfusion, several studies have observed a preserved or even elevated renal blood flow in septic patients with AKI [88, 89]. Despite an increase in renal blood flow, renal function may be impaired. An alteration in intrarenal circulation due to vasodilatation of the efferent arteriole is more prone to be responsible for AKI than a global reduction in renal blood flow. Inflammatory mediators play an important role too. Tubular epithelial cells express TLRs and can produce various pro-inflammatory mediators (e.g. IL-6, IL-8, monocyte chemoactive protein) [89]. LPS can directly cause tubular cell apoptosis through Fas-mediated and caspase-mediated pathways and have the capability of downregulating ion transport channels of the renal tubular epithelial cells [90, 91]. TNF and IL-1 is responsible for dysfunction for Na^+/K^+ pump alteration in medullary and cortical renal cells as well. The loss of ability to maintain compositionally distinct fluid-filled compartment contributes to kidney dysfunction. Even more, dendritic cell and macrophages of the kidney show antigen-presenting properties and consequently have the capacity of modulating the local immune response to DAMPs and PAMs.

2.3.5 Brain

Septic encephalopathy (SE) is characterized by acute alterations of the level of consciousness and/or delirium in a patient with sepsis [74]. Even more, sepsis survivors can develop a long-term cognitive impairment, including alteration in memory, attention and cognitive function. The mechanism of brain dysfunction remains partially understood. SE is often completely reversible suggesting a functional aetiology. Noteworthy, cross-talk between the immunoinflammatory system, nervous system and endocrine system exists [92]. This interaction represents an important component of the host response during sepsis. However, this physiological response can become unregulated and create an uncontrolled, unbinding loop leading to organ failure [93].

The major cells involved in the pathogenesis of neurological dysfunction are the cell forming the blood-brain barrier (BBB); cerebral microvascular endothelium, astrocytes, pericytes, neurons and matrix [94]. Inflammatory mediators can damage these cells leading to neurological dysfunction. In fact, pro-inflammatory cytokines and ROS can cause disruption of the tight junction between endothelial cell, astrocytes and pericytes. The increased permeability of BBB allows the entrance of circulating inflammatory mediators (e.g. TNF-α). TNF-α, which can be produced by the brain itself, can play a crucial role in the pathogenesis of SE. In fact, TNF-α regulates aquaporin 4 (AQP4) thus altering the transport of water into the brain with consequent oedema [95]. Even more, TNF-α promotes neutrophils infiltration and apoptosis cell death. Above all, oxidative stress seems to have the most important effects on cognitive impairment. Some trials have demonstrated that antioxidant treatment could significantly ameliorate the development of long- term cognitive deficits after sepsis [96].

2.4 Immunomonitoring and Immunotherapy

Since MOF is characterized by a remarkably complex inflammatory response, over the years, researchers tried to identify possible biomarkers aimed to facilitate diagnosis, guide therapy and stratify patients' clinical risk. Consequently, the concept of immunomonitoring and immunotherapy (i.e. target therapy) has emerged in recent years [97, 98]. Therefore, immunological monitoring can be useful to define the most appropriate type of therapy. Even more, cytokines levels in the plasma of trauma patients can be predictors of the development of MOF and correlate with the outcome; high levels of TNF and low levels of IL-10 correlates with high mortality [99, 100]. Not only, the measurement of the level of expression of markers on the cell surface (e.g. HLA-DR on monocytes), has emerged as a new important step in the understanding of the development of MOF [97].

Above all, Cytofluorimetry represents a useful diagnostic technique capable to identify the alterations of the immune cells and consequently the immunophenotypic changes in these cells during sepsis [99]. With the aid of Cytofluorimetry, it is now possible to measure the expression of CD64 on neutrophils, the expression of HLA-DR on monocytes and percentage of circulating regulatory T lymphocytes. The HLA system molecules are involved in the presentation of antigen to the CD4 + T lymphocytes, leading to the activation of T lymphocytes and therefore the triggering of the adaptive immune response [101]. The HLA system is characterized by a remarkable polymorphism and a consequent great variability for HLA to bind different antigens and activate an effective defence against a new insult [102]. Based on several studies, the level of expression mHLA-DR has been considered as a predictor of septic complications following various types of insults (e.g. trauma, burns, major surgery) and are predictive of mortality [103]. mHLA-DR levels can be used to assess the status of immunosuppression. Patients with reduced levels of mHLA-DR should be considered immunosuppressed and therefore could benefit from strategies aimed at reducing the risk of infection in order to avoid nosocomial infection. Furthermore, it is possible to measure the plasma concentrations of several

mediators. Numerous correlations have been observed between the increased concentration of a particular circulating mediator and unfavourable outcome, but none of these is routinely used to stage and monitor patients [59]. TNF-α, IL6 and IL8 have been extensively investigated during the last two decades [100, 104]. A high IL10 / TNF-α ratio is associated with a poor outcome. However, it should be noted that the measurement of concentrations of a single mediator to establish the immune status of patients remains questionable because it provides only a partial view of the disease [100]. An alternative can be the dosage of a markers panel rather than a single parameter, which allows a better definition of pro / anti-inflammatory profiles.

The increasing evidence on the presence of a state of immunoparalysis during sepsis makes it reasonable to shift the therapeutic target to regulate the patient's immune system [100]. It is an important prerequisite to systematically assess the immune response of patients and, consequently, to define the most suitable immunotherapies for each individual patient in a given time of illness [100]. Strategies that employ anti-inflammatory mediators (i.e. IL-10) or therapeutic strategies aimed at downregulating the inflammatory cytokine production as therapeutic agents can have a role in this field. Therefore it is rational to use, as a guide to treatment, immunological markers that give us a picture of the immune dysfunction and to evaluate both the accuracy and the effectiveness of the therapy [105].

Possible therapeutic strategies consists but are not limited to:

- Block of soluble anti-inflammatory mediators (e.g. TNF, IL-6, IL-8) [57, 69, 106];
- CD11/CD18 blockade [107];
- inhibitors of the NF-κB [108];
- p38 inhibitors [109];
- caspase-3 inhibitor [110],
- TLR agonists [108, 111];
- TLR antagonists [112];
- Silencing Fas and FasL [63];
- rhAPC [64];
- Restoration of monocyte function (e.g. INFγ, G-CSF and GM-CSF) [113, 114];
- Restoration of lymphocyte functions (IL-7 for T and lymphocytes) [115];
- Antioxidants (e.g. vitamin C, vitamin E, N-acetylcysteine) [116, 117].

Furthermore, also glucocorticoids can play a role due to its effects on interfering with various signalling pathways. Glucocorticoids can also interference with signal transduction, and modulation of RNA stability [118]. In fact, glucocorticoids bind to the intracellular glucocorticoid receptor and subsequently translocate to the nucleus, and activate anti-inflammatory pathway. Another major mechanism of action of glucocorticoids is repression of pro-inflammatory genes, through inhibition of TLR-induced pro-inflammatory signalling (via MAPK, NF-κB and IRF pathways). Regardless of these anti-inflammatory properties, the adverse effects of glucocorticoids and their profound interference with several physiological systems is always to keep in mind.

2.5 Conclusions

MOF remains a major complication after a variety of different injuries, such as trauma and sepsis, with high mobility and mortality burden. The pathogenesis of MOF remains partly comprehended. Further understanding of cell mechanism involved in the pathophysiology of MOF is vital to develop novel immunomonitoring and immunotherapy strategy with the aim of modulating the inflammatory response. Since nosocomial and iatrogenic factors have a central role in the development and in the worsening of MOF, careful selection of clinical strategy would represent one of the future major challenges for the prevention and the treatment of MOF.

References

1. Baue AE. Multiple, progressive, or sequential systems failure. A syndrome of the 1970s. Arch Surg (Chicago, Il: 1960). 1975;110(7):779–81.
2. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM consensus conference committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644–55. https://doi.org/10.1378/chest.101.6.1644.
3. Dewar D, Moore FA, Moore EE, Balogh Z. Postinjury multiple organ failure. Injury. 2009;40(9):912–8. https://doi.org/10.1016/j.injury.2009.05.024.
4. Antonelli M, Caricato A. Post-injury multiple organ failure and late outcome. Is it just an association? Critical care (London, England). 2007;11(5):166. https://doi.org/10.1186/cc6132.
5. Llompart-Pou JA, Talayero M, Homar J, Royo C. Multiorgan failure in the serious trauma patient. Med Intensiva. 2014;38(7):455–62. https://doi.org/10.1016/j.medin.2014.05.004.
6. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. A 12-year prospective study of postinjury multiple organ failure: has anything changed? Archives of surgery (Chicago, IL: 1960). 2005;140(5):432–8.; discussion 8-40. https://doi.org/10.1001/archsurg.140.5.432.
7. Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, et al. Epidemiology of trauma deaths: a reassessment. J Trauma. 1995;38(2):185–93.
8. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29(7):1303–10.
9. Tsukamoto T, Chanthaphavong RS, Pape HC. Current theories on the pathophysiology of multiple organ failure after trauma. Injury. 2010;41(1):21–6. https://doi.org/10.1016/j.injury.2009.07.010.
10. Qiu P, Wang L, Ni J, Zhang Y. Associations between HMGB1 gene polymorphisms and susceptibility and clinical outcomes in Chinese Han sepsis patients. Gene. 2019;687:23–9. https://doi.org/10.1016/j.gene.2018.11.027.
11. Liu Y, Zhao YS. Multiple organ dysfunction syndrome and related genetic polymorphisms. Zhongguo wei zhong bing ji jiu yi xue = Chinese critical care medicine = Zhongguo weizhongbing jijiuyixue. 2011;23(11):699–702.
12. Sapan HB, Paturusi I, Islam AA, Yusuf I, Patellongi I, Massi MN, et al. Interleukin-6 and interleukin-10 plasma levels and mRNA expression in polytrauma patients. Chin J Traumatol. 2017;20(6):318–22. https://doi.org/10.1016/j.cjtee.2017.05.003.
13. Virzì GM, Day S, de Cal M, Vescovo G, Ronco C. Heart–kidney crosstalk and role of humoral signaling in critical illness. Crit Care. 2014;18(1):201. https://doi.org/10.1186/cc13177.

14. Saadia R, Schein M. Multiple organ failure. How valid is the "two hit" model? J Accid Emerg Med. 1999;16(3):163–7.
15. Wang H, Ma S. The cytokine storm and factors determining the sequence and severity of organ dysfunction in multiple organ dysfunction syndrome. Am J Emerg Med. 2008;26(6):711–5. https://doi.org/10.1016/j.ajem.2007.10.031.
16. Chinnaiyan AM, Huber-Lang M, Kumar-Sinha C, Barrette TR, Shankar-Sinha S, Sarma VJ, et al. Molecular signatures of sepsis: multiorgan gene expression profiles of systemic inflammation. Am J Pathol. 2001;159(4):1199–209. https://doi.org/10.1016/s0002-9440(10)62505-9.
17. Namath A, Patterson AJ. Genetic polymorphisms in sepsis. Crit Care Nurs Clin North Am. 2011;23(1):181–202. https://doi.org/10.1016/j.ccell.2010.12.011.
18. Namath A, Patterson AJ. Genetic polymorphisms in sepsis. Crit Care Clin. 2009;25(4):835–56. https://doi.org/10.1016/j.ccc.2009.06.004.
19. van der Poll T. Immunotherapy of sepsis. Lancet Infect Dis. 2001;1(3):165–74. https://doi.org/10.1016/s1473-3099(01)00093-7.
20. Dellinger RP, Bagshaw SM, Antonelli M, Foster DM, Klein DJ, Marshall JC, et al. Effect of targeted Polymyxin B Hemoperfusion on 28-Day mortality in patients with septic shock and elevated endotoxin level: the EUPHRATES randomized clinical trial. JAMA. 2018;320(14):1455–63. https://doi.org/10.1001/jama.2018.14618.
21. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2018;9(6):7204–18. https://doi.org/10.18632/oncotarget.23208.
22. Rajaee A, Barnett R, Cheadle WG. Pathogen- and danger-associated molecular patterns and the cytokine response in sepsis. Surg Infect. 2018;19(2):107–16. https://doi.org/10.1089/sur.2017.264.
23. Iskander KN, Osuchowski MF, Stearns-Kurosawa DJ, Kurosawa S, Stepien D, Valentine C, et al. Sepsis: multiple abnormalities, heterogeneous responses, and evolving understanding. Physiol Rev. 2013;93(3):1247–88. https://doi.org/10.1152/physrev.00037.2012.
24. Kawai T, Akira S. The roles of TLRs, RLRs and NLRs in pathogen recognition. Int Immunol. 2009;21(4):317–37. https://doi.org/10.1093/intimm/dxp017.
25. Ye Z, Ting JP. NLR, the nucleotide-binding domain leucine-rich repeat containing gene family. Curr Opin Immunol. 2008;20(1):3–9. https://doi.org/10.1016/j.coi.2008.01.003.
26. Jiang Z, Georgel P, Du X, Shamel L, Sovath S, Mudd S, et al. CD14 is required for MyD88-independent LPS signaling. Nat Immunol. 2005;6(6):565–70. https://doi.org/10.1038/ni1207.
27. Latz E, Schoenemeyer A, Visintin A, Fitzgerald KA, Monks BG, Knetter CF, et al. TLR9 signals after translocating from the ER to CpG DNA in the lysosome. Nat Immunol. 2004;5(2):190–8. https://doi.org/10.1038/ni1028.
28. Wang T, Town T, Alexopoulou L, Anderson JF, Fikrig E, Flavell RA. Toll-like receptor 3 mediates West Nile virus entry into the brain causing lethal encephalitis. Nat Med. 2004;10(12):1366–73. https://doi.org/10.1038/nm1140.
29. Mogensen TH. Pathogen recognition and inflammatory signaling in innate immune defenses. Clin Microbiol Rev. 2009;22(2):240–73. https://doi.org/10.1128/cmr.00046-08.
30. Grazioli S, Pugin J. Mitochondrial damage-associated molecular patterns: from inflammatory signaling to human diseases. Front Immunol. 2018;9 https://doi.org/10.3389/fimmu.2018.00832.
31. Land WG. The role of damage-associated molecular patterns (DAMPs) in human diseases: part II: DAMPs as diagnostics, prognostics and therapeutics in clinical medicine. Sultan Qaboos Univ Med J. 2015;15(2):e157–70.
32. Chen X, Zhao HX, Bai C, Zhou XY. Blockade of high-mobility group box 1 attenuates intestinal mucosal barrier dysfunction in experimental acute pancreatitis. Sci Rep. 2017;7 https://doi.org/10.1038/s41598-017-07094-y.
33. Ferro V. Heparan sulfate inhibitors and their therapeutic implications in inflammatory illnesses. Expert Opin Ther Targets. 2013;17(8):965–75. https://doi.org/10.1517/14728222.2013.811491.

34. Ince C, Mayeux PR, Nguyen T, Gomez H, Kellum JA, Ospina-Tascon GA, et al. The endothelium in sepsis. Shock (Augusta, Ga). 2016;45(3):259–70. https://doi.org/10.1097/shk.0000000000000473.
35. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014;6(10) https://doi.org/10.1101/cshperspect.a016295.
36. Markiewski MM, DeAngelis RA, Lambris JD. Complexity of complement activation in sepsis. J Cell Mol Med. 2008;12(6a):2245–54. https://doi.org/10.1111/j.1582-4934.2008.00504.x.
37. Ward PA. Role of C5 activation products in sepsis. TheScientificWorldJOURNAL. 2010;10:2395–402. https://doi.org/10.1100/tsw.2010.216.
38. Lupu F, Keshari RS, Lambris JD, Coggeshall KM. Crosstalk between the coagulation and complement systems in sepsis. Thromb Res. 2014;133(Suppl 1):S28–31. https://doi.org/10.1016/j.thromres.2014.03.014.
39. Levi M, van der Poll T. Inflammation and coagulation. Crit Care Med. 2010;38(2 Suppl):S26–34. https://doi.org/10.1097/CCM.0b013e3181c98d21.
40. Levi M. The coagulant response in sepsis and inflammation. Hamostaseologie. 2010;30(1):10–6.
41. Semeraro N, Ammollo CT, Semeraro F, Colucci M. Sepsis, thrombosis and organ dysfunction. Thromb Res. 2012;129(3):290–5. https://doi.org/10.1016/j.thromres.2011.10.013.
42. Muenzer JT, Davis CG, Dunne BS, Unsinger J, Dunne WM, Hotchkiss RS. Pneumonia after cecal ligation and puncture: a clinically relevant "two-hit" model of sepsis. Shock (Augusta, Ga). 2006;26(6):565–70. https://doi.org/10.1097/01.shk.0000235130.82363.ed.
43. Villar J, Blanco J, Zhang H, Slutsky AS. Ventilator-induced lung injury and sepsis: two sides of the same coin? Minerva Anestesiol. 2011;77(6):647–53.
44. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS. Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. J Clin Invest. 1997;99(5):944–52. https://doi.org/10.1172/jci119259.
45. Wilson MR, Takata M. Inflammatory mechanisms of ventilator-induced lung injury: a time to stop and think? Anaesthesia. 2013;68(2):175–8. https://doi.org/10.1111/anae.12085.
46. Weinberg JA, McGwin G Jr, Griffin RL, Huynh VQ, Cherry SA 3rd, Marques MB, et al. Age of transfused blood: an independent predictor of mortality despite universal leukoreduction. J Trauma. 2008;65(2):279–82.; discussion 82–4. https://doi.org/10.1097/TA.0b013e31817c9687.
47. Watson GA, Sperry JL, Rosengart MR, Minei JP, Harbrecht BG, Moore EE, et al. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. J Trauma. 2009;67(2):221–7.; discussion 8-30. https://doi.org/10.1097/TA.0b013e3181ad5957.
48. Fink MP. Intestinal epithelial hyperpermeability: update on the pathogenesis of gut mucosal barrier dysfunction in critical illness. Curr Opin Crit Care. 2003;9(2):143–51.
49. Wolf HM, Fischer MB, Puhringer H, Samstag A, Vogel E, Eibl MM. Human serum IgA downregulates the release of inflammatory cytokines (tumor necrosis factor-alpha, interleukin-6) in human monocytes. Blood. 1994;83(5):1278–88.
50. Fukatsu K, Sakamoto S, Hara E, Ueno C, Maeshima Y, Matsumoto I, et al. Gut ischemia-reperfusion affects gut mucosal immunity: a possible mechanism for infectious complications after severe surgical insults. Crit Care Med. 2006;34(1):182–7.
51. Moore EE. Splanchnic Hypoperfusion provokes acute lung injury via a 5-lipoxygenase dependent mechanism. Am J Surg. 2010;200(6):681–9. https://doi.org/10.1016/j.amjsurg.2010.05.010.
52. Mukhopadhyay S, Hoidal JR, Mukherjee TK. Role of TNFalpha in pulmonary pathophysiology. Respir Res. 2006;7:125. https://doi.org/10.1186/1465-9921-7-125.
53. Abraham E. Neutrophils and acute lung injury. Crit Care Med. 2003;31(4 Suppl):S195–9. https://doi.org/10.1097/01.ccm.0000057843.47705.e8.
54. Lee WL, Downey GP. Neutrophil activation and acute lung injury. Curr Opin Crit Care. 2001;7(1):1–7.

55. Yang KY, Arcaroli JJ, Abraham E. Early alterations in neutrophil activation are associated with outcome in acute lung injury. Am J Respir Crit Care Med. 2003;167(11):1567–74. https://doi.org/10.1164/rccm.200207-664OC.
56. Bohrer H, Qiu F, Zimmermann T, Zhang Y, Jllmer T, Mannel D, et al. Role of NFkappaB in the mortality of sepsis. J Clin Invest. 1997;100(5):972–85. https://doi.org/10.1172/jci119648.
57. Malaviya R, Laskin JD, Laskin DL. Anti-TNFalpha therapy in inflammatory lung diseases. Pharmacol Ther. 2017;180:90–8. https://doi.org/10.1016/j.pharmthera.2017.06.008.
58. Bhatia M, Moochhala S. Role of inflammatory mediators in the pathophysiology of acute respiratory distress syndrome. J Pathol. 2004;202(2):145–56. https://doi.org/10.1002/path.1491.
59. Bozza FA, Salluh JI, Japiassu AM, Soares M, Assis EF, Gomes RN, et al. Cytokine profiles as markers of disease severity in sepsis: a multiplex analysis. Crit Care. 2007;11(2):R49. https://doi.org/10.1186/cc5783.
60. Creagh-Brown BC, Quinlan GJ, Evans TW, Burke-Gaffney A. The RAGE axis in systemic inflammation, acute lung injury and myocardial dysfunction: an important therapeutic target? Intensive Care Med. 2010;36(10):1644–56. https://doi.org/10.1007/s00134-010-1952-z.
61. Guo WA, Knight PR, Raghavendran K. The receptor for advanced glycation end products and acute lung injury/acute respiratory distress syndrome. Intensive Care Med. 2012;38(10):1588–98. https://doi.org/10.1007/s00134-012-2624-y.
62. Albertine KH, Soulier MF, Wang Z, Ishizaka A, Hashimoto S, Zimmerman GA, et al. Fas and fas ligand are up-regulated in pulmonary edema fluid and lung tissue of patients with acute lung injury and the acute respiratory distress syndrome. Am J Pathol. 2002;161(5):1783–96. https://doi.org/10.1016/s0002-9440(10)64455-0.
63. Matsuda N, Yamamoto S, Takano K, Kageyama S, Kurobe Y, Yoshihara Y, et al. Silencing of fas-associated death domain protects mice from septic lung inflammation and apoptosis. Am J Respir Crit Care Med. 2009;179(9):806–15. https://doi.org/10.1164/rccm.200804-534OC.
64. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med. 2001;344(10):699–709. https://doi.org/10.1056/nejm200103083441001.
65. Vieillard-Baron A. Septic cardiomyopathy. Ann Intensive Care. 2011;1(1):6. https://doi.org/10.1186/2110-5820-1-6.
66. Hochstadt A, Meroz Y, Landesberg G. Myocardial dysfunction in severe sepsis and septic shock: more questions than answers? J Cardiothorac Vasc Anesth. 2011;25(3):526–35. https://doi.org/10.1053/j.jvca.2010.11.026.
67. Weisel RD, Vito L, Dennis RC, Valeri CR, Hechtman HB. Myocardial depression during sepsis. Am J Surg. 1977;133(4):512–21.
68. Bujak M, Frangogiannis NG. The role of IL-1 in the pathogenesis of heart disease. Arch Immunol Ther Exp. 2009;57(3):165–76. https://doi.org/10.1007/s00005-009-0024-y.
69. Vincent JL, Bakker J, Marecaux G, Schandene L, Kahn RJ, Dupont E. Administration of anti-TNF antibody improves left ventricular function in septic shock patients. Results Pilot Study Chest. 1992;101(3):810–5. https://doi.org/10.1378/chest.101.3.810.
70. Markel TA, Crisostomo PR, Wang M, Herrmann JL, Abarbanell AM, Meldrum DR. Right ventricular TNF resistance during endotoxemia: the differential effects on ventricular function. Am J Physiol Regul Integr Comp Physiol. 2007;293(5):R1893–7. https://doi.org/10.1152/ajpregu.00359.2007.
71. Pathan N, Franklin JL, Eleftherohorinou H, Wright VJ, Hemingway CA, Waddell SJ, et al. Myocardial depressant effects of interleukin 6 in meningococcal sepsis are regulated by p38 mitogen-activated protein kinase. Crit Care Med. 2011;39(7):1692–711. https://doi.org/10.1097/CCM.0b013e3182186d27.
72. Stengl M, Bartak F, Sykora R, Chvojka J, Benes J, Krouzecky A, et al. Reduced L-type calcium current in ventricular myocytes from pigs with hyperdynamic septic shock. Crit Care Med. 2010;38(2):579–87. https://doi.org/10.1097/CCM.0b013e3181cb0f61.

73. Cariou A, Pinsky MR, Monchi M, Laurent I, Vinsonneau C, Chiche JD, et al. Is myocardial adrenergic responsiveness depressed in human septic shock? Intensive Care Med. 2008;34(5):917–22. https://doi.org/10.1007/s00134-008-1022-y.
74. Sharshar T, Annane D, de la Grandmaison GL, Brouland JP, Hopkinson NS, Francoise G. The neuropathology of septic shock. Brain Pathol (Zurich, Switzerland). 2004;14(1):21–33.
75. Brienza N, Ayuse T, Revelly JP, O'Donnell CP, Robotham JL. Effects of endotoxin on isolated porcine liver: pressure-flow analysis. J Appl Physiol (Bethesda, Md: 1985). 1995;78(3):784–92. https://doi.org/10.1152/jappl.1995.78.3.784.
76. Dahn MS, Lange P, Lobdell K, Hans B, Jacobs LA, Mitchell RA. Splanchnic and total body oxygen consumption differences in septic and injured patients. Surgery. 1987;101(1):69–80.
77. Levy B, Collin S, Sennoun N, Ducrocq N, Kimmoun A, Asfar P, et al. Vascular hyporesponsiveness to vasopressors in septic shock: from bench to bedside. Intensive Care Med. 2010;36(12):2019–29. https://doi.org/10.1007/s00134-010-2045-8.
78. Bucher M, Hobbhahn J, Taeger K, Kurtz A. Cytokine-mediated downregulation of vasopressin V(1A) receptors during acute endotoxemia in rats. Am J Physiol Regul Integr Comp Physiol. 2002;282(4):R979–84. https://doi.org/10.1152/ajpregu.00520.2001.
79. Wang D, Yin Y, Yao Y. Advances in sepsis-associated liver dysfunction. Burns Trauma. 2014;2(3):97–105. https://doi.org/10.4103/2321-3868.132689.
80. Arii S, Imamura M. Physiological role of sinusoidal endothelial cells and Kupffer cells and their implication in the pathogenesis of liver injury. J Hepato-Biliary-Pancreat Surg. 2000;7(1):40–8. https://doi.org/10.1007/s005340000070040.534.
81. Koo DJ, Chaudry IH, Wang P. Kupffer cells are responsible for producing inflammatory cytokines and hepatocellular dysfunction during early sepsis. J Surg Res. 1999;83(2):151–7. https://doi.org/10.1006/jsre.1999.5584.
82. Yang S, Zhou M, Chaudry IH, Wang P. Norepinephrine-induced hepatocellular dysfunction in early sepsis is mediated by activation of alpha2-adrenoceptors. Am J Physiol Gastrointest Liver Physiol. 2001;281(4):G1014–21. https://doi.org/10.1152/ajpgi.2001.281.4.G1014.
83. Ananian P, Hardwigsen J, Bernard D, Le Treut YP. Serum acute-phase protein level as indicator for liver failure after liver resection. Hepato-Gastroenterology. 2005;52(63):857–61.
84. Diao L, Li N, Brayman TG, Hotz KJ, Lai Y. Regulation of MRP2/ABCC2 and BSEP/ABCB11 expression in sandwich cultured human and rat hepatocytes exposed to inflammatory cytokines TNF-{alpha}, IL-6, and IL-1{beta}. J Biol Chem. 2010;285(41):31185–92. https://doi.org/10.1074/jbc.M110.107805.
85. Dhainaut JF, Marin N, Mignon A, Vinsonneau C. Hepatic response to sepsis: interaction between coagulation and inflammatory processes. Crit Care Med. 2001;29(7 Suppl):S42–7.
86. Boehme MW, Galle P, Stremmel W. Kinetics of thrombomodulin release and endothelial cell injury by neutrophil-derived proteases and oxygen radicals. Immunology. 2002;107(3):340–9. https://doi.org/10.1046/j.1365-2567.2002.01469.x.
87. Knolle PA, Loser E, Protzer U, Duchmann R, Schmitt E, Zum Buschenfelde KH, et al. Regulation of endotoxin-induced IL-6 production in liver sinusoidal endothelial cells and Kupffer cells by IL-10. Clin Exp Immunol. 1997;107(3):555–61. https://doi.org/10.1046/j.1365-2249.1997.d01-959.x.
88. Brenner M, Schaer GL, Mallory DL, Suffredini AF, Parrillo JE. Detection of renal blood flow abnormalities in septic and critically ill patients using a newly designed indwelling thermodilution renal vein catheter. Chest. 1990;98(1):170–9. https://doi.org/10.1378/chest.98.1.170.
89. Rector F, Goyal S, Rosenberg IK, Lucas CE. Sepsis: a mechanism for vasodilatation in the kidney. Ann Surg. 1973;178(2):222–6. https://doi.org/10.1097/00000658-197308000-00021.
90. Schmidt C, Hocherl K, Schweda F, Kurtz A, Bucher M. Regulation of renal sodium transporters during severe inflammation. J Am Soc Nephrol. 2007;18(4):1072–83. https://doi.org/10.1681/asn.2006050454.
91. Olesen ET, de Seigneux S, Wang G, Lutken SC, Frokiaer J, Kwon TH, et al. Rapid and segmental specific dysregulation of AQP2, S256-pAQP2 and renal sodium transporters in

rats with LPS-induced endotoxaemia. Nephrol Dial Transpl. 2009;24(8):2338–49. https://doi.org/10.1093/ndt/gfp011.
92. Seely AJ, Christou NV. Multiple organ dysfunction syndrome: exploring the paradigm of complex nonlinear systems. Crit Care Med. 2000;28(7):2193–200.
93. Streck EL, Comim CM, Barichello T, Quevedo J. The septic brain. Neurochem Res. 2008;33(11):2171–7. https://doi.org/10.1007/s11064-008-9671-3.
94. Abbott NJ, Ronnback L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. Nat Rev Neurosci. 2006;7(1):41–53. https://doi.org/10.1038/nrn1824.
95. Alexander JJ, Jacob A, Cunningham P, Hensley L, Quigg RJ. TNF is a key mediator of septic encephalopathy acting through its receptor, TNF receptor-1. Neurochem Int. 2008;52(3):447–56. https://doi.org/10.1016/j.neuint.2007.08.006.
96. Della Giustina A, Goldim MP, Danielski LG, Florentino D, Mathias K, Garbossa L, et al. Alpha-lipoic acid attenuates acute neuroinflammation and long-term cognitive impairment after polymicrobial sepsis. Neurochem Int. 2017;108:436–47. https://doi.org/10.1016/j.neuint.2017.06.003.
97. Leentjens J, Kox M, Pickkers P. Immunomodulation for sepsis: a change of tack? Ned Tijdschr Geneeskd. 2014;158:A6859.
98. Hamers L, Kox M, Pickkers P. Sepsis-induced immunoparalysis: mechanisms, markers, and treatment options. Minerva Anestesiol. 2015;81(4):426–39.
99. Daix T, Guerin E, Tavernier E, Mercier E, Gissot V, Herault O, et al. Multicentric standardized flow cytometry routine assessment of patients with sepsis to predict clinical worsening. Chest. 2018;154(3):617–27. https://doi.org/10.1016/j.chest.2018.03.058.
100. Peters van Ton AM, Kox M, Abdo WF, Pickkers P. Precision immunotherapy for sepsis. Front Immunol. 2018;9 https://doi.org/10.3389/fimmu.2018.01926.
101. Kessel A, Bamberger E, Masalha M, Toubi E. The role of T regulatory cells in human sepsis. J Autoimmun. 2009;32(3–4):211–5. https://doi.org/10.1016/j.jaut.2009.02.014.
102. Jin P, Wang E. Polymorphism in clinical immunology – from HLA typing to immunogenetic profiling. J Transl Med. 2003;1:8. https://doi.org/10.1186/1479-5876-1-8.
103. Faix JD. Biomarkers of sepsis. Crit Rev Clin Lab Sci. 2013;50(1):23–36. https://doi.org/10.3109/10408363.2013.764490.
104. Patel RT, Deen KI, Youngs D, Warwick J, Keighley MR. Interleukin 6 is a prognostic indicator of outcome in severe intra-abdominal sepsis. Br J Surg. 1994;81(9):1306–8.
105. Venet F, Lukaszewicz AC, Payen D, Hotchkiss R, Monneret G. Monitoring the immune response in sepsis: a rational approach to administration of immunoadjuvant therapies. Curr Opin Immunol. 2013;25(4):477–83. https://doi.org/10.1016/j.coi.2013.05.006.
106. Opal SM, Fisher CJ Jr, Dhainaut JF, Vincent JL, Brase R, Lowry SF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. The Interleukin-1 receptor antagonist sepsis Investigator Group. Crit Care Med. 1997;25(7):1115–24.
107. Faxon DP, Gibbons RJ, Chronos NA, Gurbel PA, Sheehan F. The effect of blockade of the CD11/CD18 integrin receptor on infarct size in patients with acute myocardial infarction treated with direct angioplasty: the results of the HALT-MI study. J Am Coll Cardiol. 2002;40(7):1199–204.
108. Kasinski AL, Du Y, Thomas SL, Zhao J, Sun SY, Khuri FR, et al. Inhibition of IkappaB kinase-nuclear factor-kappaB signaling pathway by 3,5-bis(2-flurobenzylidene)piperidin-4-one (EF24), a novel monoketone analog of curcumin. Mol Pharmacol. 2008;74(3):654–61. https://doi.org/10.1124/mol.108.046201.
109. Gangwal RP, Bhadauriya A, Damre MV, Dhoke GV, Sangamwar AT. p38 mitogen-activated protein kinase inhibitors: a review on pharmacophore mapping and QSAR studies. Curr Top Med Chem. 2013;13(9):1015–35.
110. Hotchkiss RS, Chang KC, Swanson PE, Tinsley KW, Hui JJ, Klender P, et al. Caspase inhibitors improve survival in sepsis: a critical role of the lymphocyte. Nat Immunol. 2000;1(6):496–501. https://doi.org/10.1038/82741.

111. Parkinson T. The future of toll-like receptor therapeutics. Curr Opin Mol Ther. 2008;10(1):21–31.
112. Patra MC, Choi S. Recent progress in the development of toll-like receptor (TLR) antagonists. Expert Opin Ther Pat. 2016;26(6):719–30. https://doi.org/10.1080/13543776.2016.1185415.
113. Bo L, Wang F, Zhu J, Li J, Deng X. Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) for sepsis: a meta-analysis. Crit Care. 2011;15(1):R58. https://doi.org/10.1186/cc10031.
114. Delsing CE, Gresnigt MS, Leentjens J, Preijers F, Frager FA, Kox M, et al. Interferon-gamma as adjunctive immunotherapy for invasive fungal infections: a case series. BMC Infect Dis. 2014;14:166. https://doi.org/10.1186/1471-2334-14-166.
115. Francois B, Jeannet R, Daix T, Walton AH, Shotwell MS, Unsinger J, et al. Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial. JCI. Insight. 2018;3(5) https://doi.org/10.1172/jci.insight.98960.
116. Porter JM, Ivatury RR, Azimuddin K, Swami R. Antioxidant therapy in the prevention of organ dysfunction syndrome and infectious complications after trauma: early results of a prospective randomized study. Am Surg. 1999;65(5):478–83.
117. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: a retrospective before-after study. Chest. 2017;151(6):1229–38. https://doi.org/10.1016/j.chest.2016.11.036.
118. Ratman D, Vanden Berghe W, Dejager L, Libert C, Tavernier J, Beck IM, et al. How glucocorticoid receptors modulate the activity of other transcription factors: a scope beyond tethering. Mol Cell Endocrinol. 2013;380(1–2):41–54. https://doi.org/10.1016/j.mce.2012.12.014.

Multiple Organ Failure Epidemiology

3

Hannah Black

3.1 Introduction

There are different scoring systems and different time points used to define MOF. The definition can vary significantly across institutions and research studies. Incidence estimates also vary depending on the patient cohort, following sepsis, trauma, or Intensive Care Unit (ICU) admission [1]. Over recent years, the nature and incidence of MOF has been changing due to advanced resuscitation practices, trauma systems, acute care and more patients surviving their initial injuries. The previous model was a bimodal development constituting early and late MOF; however, research has explored differing patterns of progression, severity, and outcomes as a result of improvements in resuscitation and care [2].

3.2 Incidence

The exact epidemiology of MOF remains unclear as the incidence varies between studies from as low as single digits to as high as 86%. The precise incidence of MOF is difficult to determine as there is no consensus for the definition. As such, the incidence of MOF varies considerably between studies which use different scoring systems. While differences in inclusion criteria, therapeutic approach, trauma systems, and year of data collection may contribute to some variation in incidence, most of these studies were conducted in developed trauma systems and examined a severely injured patient cohort. Therefore, some of this variation must be due to the disparity and difficulty defining MOF [3].

H. Black (✉)
John Hunter Hospital, New Lambton Heights, NSW, Australia

School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia
e-mail: hannah.black@uon.edu.au

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_3

Out of the United States incidence of MOF ranges from 15% reported in the early 1990s [4] to 25% in the early 2000s [5–7] to 29% in 2012 [8]. Studies from Europe report a higher range between 20% and 86% [9–14]. Few studies have been conducted in Australia to determine the incidence of MOF in severely injured trauma patients. Dewar et al. (2013) found a MOF incidence of 15% in an Australian population [15].

3.3 Demographics

Post-injury MOF affects males significantly more than females [7, 8, 12]. Sperry et al. (2008) found that male sex was independently associated with a 40% higher rate of MOF [16]. MOF incidence is also higher in older populations and those with a higher number of existing medical comorbidities [8, 12, 15]. An aging population may contribute to increased MOF incidence. Development of MOF is also associated with the more severely injured [17] described by both anatomical and physiological scores and higher incidence of head injuries [12]. Many MOF studies however exclude severe brain injury due to their different pattern of mortality and frequent requirement for vasoactive medication unrelated to cardiovascular function (REF). This fact also complicates the comparison of incidence from different studies.

The association with the mechanism of injury is somewhat equivocal. High injury severity subgroup of penetrating trauma can be associated with most frequent MOF, which could be partially due to the likelihood of associated major blood loss and traumatic shock requiring resuscitation (also predictor of MOF) [15]. In general, blunt trauma has a higher MOF incidence when compared to penetrating trauma of similar severity with an odds ratio of 1.7 [18].

3.4 Outcomes

Post-trauma MOF is the leading cause of late mortality in severe trauma. MOF-associated mortality rates range from as low as 3% to as high as 52% [5, 7, 9, 12, 14, 19]. MOF-associated mortality has been reported to be six times higher than non-MOF mortality [12]. MOF-associated mortality increases as the number of organs affected with the rate of mortality approaching 100% when four or more organs fail [18–21]. A survival rate of 75% 2– 7 years after discharge from the ICU has been reported with mortality up to 7 years post-injury at 42%. The presence of MOF also increased the risk of death by six times compared to patients without organ failure [10]. MOF patients had higher mortality when compared to non-MOF patients (24% vs 3%) in an Australian trauma population [15]. As well as increased mortality, MOF is associated with the development of other complications including increased risk of infections [8, 16].

Severely injured trauma patients who go on to develop MOF are treated exclusively in the ICU, requiring extensive use of hospital and ICU resources including

longer ICU length of stay (LOS), in-hospital LOS, and ventilator dependence [12, 14]. Dewar et al. (2013) found MOF patients remained in the ICU for three times longer than non-MOF patients, requiring four times the ventilator days [15]. As the population of Australia continues to age, so does the average age of trauma patients with additional comorbidities, which places an increasing burden on the healthcare system. Sauaia et al. (2017) demonstrated that in a US study MOF patients made up 9% of the total ICU population, but required 20% of the total ICU and mechanical ventilation days. Based on estimated critical care costs in the USA, MOF patients account for 22% and the median estimated cost per MOF patient was approximately double that for a non-MOF patient [22]. Ulvik et al. (2007) also demonstrated MOF patients were 3.9 times more likely to require personal assistance with daily injuries post-injury representing a significant financial and social burden [10].

Gentile et al. (2012) proposed late MOF was declining due to improvements in clinical care post-injury. They stated there had been an increase in patients who survived their initial injuries as well as initial sepsis and organ failure. These patients went on to develop prolonged immune dysfunction involving moderate organ dysfunction, secondary infection, requirement for ICU resources, and progressive protein catabolism. They termed this emerging disorder persistent inflammation, immunosuppression, and catabolism syndrome (PICS) [23].

Older trauma patients, specifically over the age of 65 years, and those with existing comorbidities are the most vulnerable to PICS. The long-term effects of PICS are the most concerning aspect of this phenotype as it often leads to poor quality of life outcomes. These patients are commonly discharged to long-term acute care facilities where sepsis requiring re-hospitalization, failure to rehabilitate, and progression to death is common. Not only do these outcomes lead to a poor quality of life for patients but put an enormous burden on the healthcare systems and those who must care for these patients. Data also suggests that while mortality is decreasing, incidence of PICS is increasing [24, 25].

3.5 Changes Over Time

MOF and associated mortality trends do not appear to be any clearer with some studies reporting a decrease in MOF associated with advances in trauma and critical care [6, 15, 21] while others claim MOF is increasing [26] as a result of these same advancements improving trauma survivability. Some studies suggest over the past decade mortality of severely injured post-trauma patients has decreased which has resulted in an increase in the incidence of MOF [12].

The majority of studies identified an increase in MOF incidence with a corresponding decrease in MOF-associated mortality. Nast-Kolb et al. (2001) found an increase in MOF incidence of 25.6% to 33.6% from 1975 to 1999. They also found MOF-associated mortality decreased from 18.0% to 4.1% while the ICU LOS did not change over the time period. The authors also noted the average age of patients dying from MOF increased from 44± 3 years to 63± 6 years [26]. Kahl et al. (2013) also found MOF-associated deaths had decreased between 2000 and 2011 [27]. One

of the largest retrospective analyses out of Europe, spanning 25 years, found the incidence of MOF increased slightly, whereas the overall mortality decreased significantly. They noted an increase in the trauma population age [26]. Fröhlich (2014) agreed that mortality overall and within the MOF cohort decreased over the decade 2002 to 2011, whereas the incidence of MOF increased in a European population [12].

There are still a number of studies that found the incidence of MOF decreased over time. From 2003 to 2010 Sauaia et al. (2014) demonstrated a decrease in MOF incidence and an increase in MOF-associated mortality over 8 years [28]. Aldrian et al. (2007) reported a decrease in MOF while the overall mortality rate remained constant [29]. In an Australian population, a decrease in MOF over 15 years was identified [15]. Ciesla et al. (2005) found the incidence of MOF nearly halved from 1992 to 2003 despite increasing injury severity. They also noted a decrease in MOF-associated mortality and duration over the study period [7].

As more patients are surviving severe trauma and their initial injuries, it is likely more patients are having the potential to develop MOF, thereby resulting in increasing MOF incidences. Also, due to higher patient survival an increased incidence of MOF may reflect more severe cases of MOF that cannot be helped by improved trauma care.

References

1. Osterbur K, Mann FA, Kuroki K, DeClue A. Multiple organ dysfunction syndrome in humans and animals. J Vet Intern Med. 2014;28(4):1141–51.
2. Cole E, Gillespie S, Vulliamy P, Brohi K. Multiple organ dysfunction after trauma. Br J Surg. 2020;107(4):402–12.
3. Sauaia A, Moore EE, Johnson JL, Ciesla DJ, Biffl WL, Banerjee A. Validation of postinjury multiple organ failure scores. Shock. 2009;31(5):438–47.
4. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC. Postinjury multiple organ failure: a bimodal phenomenon. J Trauma Acute Care Surg. 1996;40(4):501–12.
5. Durham RM, Moran JJ, Mazuski JE, Shapiro MJ, Baue AE, Flint LM. Multiple Organ Failure in Trauma Patients. J Trauma Injury Infect Crit Care. 2003;55(4):608–16.
6. Ciesla DJ, Moore EE, Johnson JL, Sauaia A, Cothren CC, Moore JB, et al. Multiple organ dysfunction during resuscitation is not postinjury multiple organ failure. Arch Surg. 2004;139(6):590–5.
7. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. A 12-year prospective study of postinjury multiple organ failure: has anything changed? Arch Surg. 2005;140(5):432–8. discussion 8–40
8. Minei JP, Cuschieri J, Sperry J, Moore EE, West MA, Harbrecht BG, et al. The changing pattern and implications of multiple organ failure after blunt injury with hemorrhagic shock. Crit Care Med. 2012;40(4):1129–35.
9. 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.
10. Ulvik A, Kvale R, Wentzel-Larsen T, Flaatten H. Multiple organ failure after trauma affects even long-term survival and functional status. Crit Care. 2007;11(5):R95.
11. Shepherd JM, Cole E, Brohi K. Contemporary patterns of multiple organ dysfunction in trauma. Shock. 2017;47(4):429–35.

12. Fröhlich M, Lefering R, Probst C, Paffrath T, Schneider MM, Maegele M, et al. Epidemiology and risk factors of multiple-organ failure after multiple trauma: an analysis of 31,154 patients from the TraumaRegister DGU. J Trauma Acute Care Surg. 2014;76(4):921–7. discussion 7-8
13. Brattström O, Granath F, Rossi P, Oldner A. Early predictors of morbidity and mortality in trauma patients treated in the intensive care unit. Acta Anaesthesiol Scand. 2010;54(8):1007–17.
14. Laudi S, Donaubauer B, Busch T, Kerner T, Bercker S, Bail H, et al. Low incidence of multiple organ failure after major trauma. Injury. 2007;38(9):1052–8.
15. Dewar DC, Tarrant SM, King KL, Balogh ZJ. Changes in the epidemiology and prediction of multiple-organ failure after injury. J Trauma Acute Care Surg. 2013;74(3):774–9.
16. Sperry JL, Friese RS, Frankel HL, West MA, Cuschieri J, Moore EE, et al. Male gender is associated with excessive IL-6 expression following severe injury. J Trauma. 2008;64(3):572–8. discussion 8–9
17. Brakenridge SC, Phelan HA, Henley SS, Golden RM, Kashner TM, Eastman AE, et al. Early blood product and crystalloid volume resuscitation: risk association with multiple organ dysfunction after severe blunt traumatic injury. J Trauma Injury Infect Critical Care. 2011;71(2):299–305.
18. Dewar D, Moore FA, Moore EE, Balogh Z. Postinjury multiple organ failure. Injury. 2009;40(9):912–8.
19. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. J Trauma. 2006;60(6 Suppl):S3–11.
20. Vogel JA, Liao MM, Hopkins E, Seleno N, Byyny RL, Moore EE, et al. Prediction of postinjury multiple-organ failure in the emergency department: development of the Denver emergency department trauma organ failure score. J Trauma Acute Care Surg. 2014;76(1):140–5.
21. Durham RM, Moran JJ, Mazuski JE, Shapiro MJ, Baue AE, Flint LM. Multiple Organ Failure in Trauma Patients. J Trauma Acute Care Surg. 2003;55(4):608–16.
22. Sauaia A, Moore FA, Moore EE. Postinjury inflammation and organ dysfunction. Crit Care Clin. 2017;33(1):167–91.
23. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. 2012;72(6):1491–501.
24. Rosenthal MD, Moore FA. Persistent inflammatory, immunosuppressed, catabolic syndrome (PICS): a new phenotype of multiple organ failure. Journal of advanced nutrition and human. Metabolism. 2015;1(1):e784.
25. Efron PA, Mohr AM, Bihorac A, Horiguchi H, Hollen MK, Segal MS, et al. Persistent inflammation, immunosuppression, and catabolism and the development of chronic critical illness after surgery. Surgery. 2018;164(2):178–84.
26. Nast-Kolb D, Aufmkolk M, Rucholtz S, Obertacke U, Waydhas C. Multiple organ failure still a major cause of morbidity but not mortality in blunt multiple trauma. J Trauma. 2001;51(5):835–41. discussion 41–2
27. Kahl JE, Calvo RY, Sise MJ, Sise CB, Thorndike JF, Shackford SR. The changing nature of death on the trauma service. J Trauma Acute Care Surg. 2013;75(2):195–201.
28. 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. J Trauma Acute Care Surg. 2014;76(3):582–92. discussion 92-3
29. Aldrian S, Koenig F, Weninger P, Vécsei V, Nau T. Characteristics of polytrauma patients between 1992 and 2002: what is changing? Injury. 2007;38(9):1059–64.

The Population at Risk Predictors of MOF

4

Kate L. King and Zsolt J. Balogh

4.1 Patient Factors

Patient factors associated with post-injury MOF have changed little over time. They are the least amenable to modification. The only real way to impact on patient factors is through primary prevention campaigns, that is to prevent the injury occurring in the first instance.

4.1.1 Age

Age and in particular advancing age, has consistently been reported as an independent risk factor for developing post-injury MOF, with many studies demonstrating that MOF patients tend to be older than non-MOF patients [1–4]. There appears to be two general cut-offs for describing 'elderly' trauma of 55 and 65 years, both of which are associated with MOF development [5]. For studies that have looked at temporal changes, the age of both the 'at risk' population and those that develop MOF has increased over time in line with our known ageing population [6, 7]. Advanced age is also an independent risk factor for mortality [8]. It is not clear if this is due to less physical reserve to deal with the insult, their comorbidities or other less defined reasons.

K. L. King (✉)
The Department of Traumatology, John Hunter Hospital, Newcastle, NSW, Australia

The University of Newcastle, Newcastle, NSW, Australia
e-mail: kate.king@health.nsw.gov.au

Z. J. Balogh
Department of Traumatology, John Hunter Hos and Univers of Newcastle, Newcastle, NSW, Australia
e-mail: Zsolt.Balogh@health.nsw.gov.au

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_4

4.1.2 Gender

Similar to age, male gender is a well-described independent risk factor for MOF and has not changed in significance since first documented. Males are more likely to develop MOF when compared to females. The female gender is actually thought to be protective against the development of MOF [9, 10]; however, females that do develop MOF have a higher mortality rate compared to their male counterparts [6].

4.1.3 Obesity

Obesity (defined as a body mass index (BMI) > 30 kg/m^2) is a global health problem. Obesity in severely injured patients is known to increase morbidity and to a lesser degree mortality [11–14]. Ciesla et al. demonstrated that obese patients are at an increased risk of developing post-injury MOF [15]. There is evidence in the non-obese (BMI >18 to <30) trauma patient population that the risk of developing MOF increases by 9% for each incremental point in the BMI [16]. The exact pathophysiology is not well understood but is thought to be related to the inflammatory mediators in the adipose tissue providing a proinflammatory environment [15].

4.1.4 Other Patient Factors

Some other novel patient factors that have been described in the literature include the use of pre-injury statins increasing the risk of post-injury MOF [17] and pre-injury antiplatelet use reducing the risk of MOF [18] and genetic predisposition to MOF [19].

4.2 Treatment Factors

Forty years ago MOF was universally fatal [20]. Management of severely injured trauma patients has evolved significantly over this period which has impacted on some of the earlier risk factors identified and predictors that were identified. Trauma care has been refined from shortly after the time of impact right through to rehabilitation. The following treatment factors have all contributed to a decreasing mortality rate associated with MOF. The impact on incidence is harder to measure due to the lack of consensus on definition which affects the epidemiological data published.

4.2.1 Fluid Resuscitation

When post-injury MOF was first being described, resuscitation practices were very different, we have learnt that fluid resuscitation is a potentially modifiable predictor in post-injury MOF. The trauma patient with haemorrhagic shock was treated with

aggressive crystalloid fluid resuscitation a hangover from our learnings during the Korean and Vietnam wars with the end point being to support blood pressure and urine output in the patient [21, 22]. With this aggressive crystalloid resuscitation we saw new complications emerging in our trauma population, it was thought to increase reperfusion injury and leukocyte adhesion [23–25]. These contributed significantly to morbidity and mortality and included syndromes such as acute respiratory distress syndrome (ARDS) [26], compartment syndromes, particularly Abdominal Compartment Syndrome (ACS) [27] and dilutional coagulopathy [28]. Clinicians researching post-injury MOF in the critically ill trauma patients were able to observe the sequelae of these traditional resuscitation practices and this allowed for refinement in practice and development of damage control resuscitation, limiting crystalloids, infusing blood and blood components in ratios that mirrored whole blood, which ultimately improved outcomes for trauma patients [29].

4.2.2 Pre-Hospital Care

Exsanguination remains the leading cause of pre-hospital trauma deaths [30]. Improvements over the last few decades in the pre-hospital phase of trauma care have been multifactorial with system design and clinical interventions. The pre-hospital team's composition varies from one country to the next and there is evidence that physician-led teams at scene improve outcomes [31]. Short scene times are beneficial in traumatic brain injuries and penetrating haemodynamically unstable patients [32]. In one study, patients receiving packed red blood cells and plasma in the pre-hospital phase had a mortality benefit, whereas those receiving crystalloids only had the worst survival [33]. Research has demonstrated that low volumes of crystalloid resuscitation in the pre-hospital phase leads to a lower incidence of MOF [34]. The final piece that allows all the advances in pre-hospital care to be beneficial to the trauma patient is a well-developed trauma system so the pre-hospital care providers can take them to the most appropriate trauma centre in the first instance. There is good evidence that patients that are taken to trauma hospitals in an inclusive trauma system have better outcomes with reported mortality rates reduced by 15–25% [35].

4.2.3 Acute Respiratory Distress Syndrome

Acute Respiratory Distress Syndrome (ARDS) in trauma has been associated with significant morbidity and mortality [36]. The incidence of ARDS in trauma patients is anywhere from 3% to 40% [37–40]. The known predictors of ARDS in trauma patients include crystalloid resuscitation, large transfusions of PRBC >10 units, plasma transfusions, blunt injuries, inhalation injuries, severity of injury, ISS > 25, female gender and hypotension [41, 42]. Advancement in organ support, particularly lung protection ventilation and haemostatic resuscitation are thought to have led to a decrease in incidence but mortality from ARDS in MOF patients is still high

[43]. However, lung failure remains the most common organ to fail in MOF patients [6, 44]. The lungs are frequently the first organs to fail [45] so it is debatable if lung failure or ARDS is a predictor of post-injury MOF or already part of the MOF picture. Chap. 12 covers respiratory failure in more depth.

4.2.4 Advancement in Organ Support in the ICU

One of the most significant changes that we have seen in the management of critically injured patients in the ICU is lung protective ventilation. It is the current standard of care for mechanical ventilation. It refers to the use of low tidal volume (VT) ventilation (4–8 mL/kg) and was first described by Amato in the late 1990s and was seen as beneficial in preventing ventilated acquired lung injury (VALI) [46, 47]. The mechanisms causing VALI are thought to be multifactorial including direct structural causes such as high inspiratory pressures (barotrauma), alveolar over distention (volutrauma) and can trigger an inflammatory response resulting in biotrauma [48]. Lung protective ventilation can entail other mechanisms in conjunction with low VT including increasing PEEP, recruitment manoeuvres and allowing for hypercapnia [49].

Another advance in medical care during this period is the use of renal replacement therapies (RRT). Acute kidney injury (AKI) is common amongst the critically ill and is associated with a significant mortality rate up to 60% [50]. The timing and commencement of RRT remains controversial [51]. However, there is some evidence that early RRT compared to late RRT improves mortality at 90 days [52].

4.2.5 Blood Transfusion

Blood transfusion is another potential modifiable risks for MOF where we have seen changes in practice over the last few decades. Blood and blood compartments transfusion have become a key component of damage control resuscitation and haemostatic resuscitation. Early use of DCR has been shown to improve patient survival and decrease length of stay of haemorrhaging patients [53].

Blood transfusion of packed red blood cell (PRBC) during the early resuscitation period is an independent risk predictor for mortality ICU admission, ICU LOS and hospital LOS for severely injured trauma patients [54, 55]. It is also well documented as a consistent and independent risk factor for the development post-injury MOF [1, 2, 56, 57]. Patel et al. in their meta-analysis article demonstrated that the odds of developing MOF increased with each additional unit of blood given (blood as a continuous variable) and a strong increased odds for those receiving >6 units of PRBC (blood as a binary variable) for developing MOF [58]. Current evidence suggests the transfusion of PRBCs has both inflammatory and immunosuppressive effects on the patient with PRBCs containing numerous immune mediators that have the potential to interact with or alter the immune response [59]. There are several other donor, storage and delivery factors that are thought to contribute to the development of MOF, including the storage age of the blood being transfused [60, 61] and donor

characteristics such as female gender donor [62]. There is also evidence that specific blood group (group A) is associated with an increased risk of ARDS [63, 64].

The development of massive transfusion protocols (MTPs) saw a reduction in mortality in both the civilian and military setting [65, 66]. Most of the survival advantage associated with MTP was thought to have come from the efficient administration of predefined, protocol driven ratios of PRBC, plasma and platelets [67–70]. MTPs improve transfusion times and volumes which is an important consideration when using a limited resource [71]. Most importantly, MTPs have been proven to reduce MOF [72]. Several studies have been recently undertaken to determine the most appropriate ratios of PRBC to platelets and plasma trying to reach a balanced transfusion in trauma. PROMMTT and PROPPR both looked at ratios and impact mortality and CRASH 2 with the introduction of tranexamic acid to resuscitation practice [73–75].

4.3 Injury Factors

Injury factors contribute to the complex aetiology of post-injury MOF. Injury severity has not changed over the years of observing the at risk population yet other injury factors such as abdominal compartment syndrome have almost disappeared during the same period [76].

4.3.1 Injury Severity

Injury severity is described throughout the literature using the anatomical descriptor Injury Severity Score (ISS). The severity of injury has consistently been described as an independent risk factor for the development of MOF [1, 77]. It is one of only a few that has remained consistent since the introduction of haemostatic resuscitation [1].

4.3.2 New Injury Severity Score

The new injury severity score (NISS) was designed by Osler in the late 1990s to address some of the limitations in calculation and prediction of the ISS [78]. NISS subsequently was proven to be superior to ISS in predicting post-injury MOF, in particular patients with a NISS higher than their ISS [79].

4.3.3 Abdominal Compartment Syndrome

Intra-abdominal pressure (IAP) and even the measuring of it has been around since the late 1800s [80]. IAP is the steady state of pressure within the abdominal cavity. When IAP is >12 mmHg, the patient has Intra-abdominal Hypertension (IAH). It took another 100 years before Abdominal Compartment Syndrome (ACS) as a

concept was first described by Kron et al. in 1984 but the actual term was coined by Fietsam et al. in 1989 when describing the syndrome in ruptured abdominal aortic aneurysms [81, 82]. ACS is defined as a sustained IAP >20 mmHg (>10 mmHg in the paediatric patient) with signs of new organ failure [83]. By the early 2000s the relatively new syndrome ACS was gaining so much attention that a World Society of the Abdominal Compartment Syndrome (WSACS) was developed in 2004. ACS was further defined as primary ACS where the patient had an actual abdominal injury and secondary ACS where there was no abdominal injury [84]. Primary ACS was thought to be a result of damage control surgery and secondary ACS to be caused from severe shock requiring massive resuscitation [85]. Initially ACS was thought to be a result of MOF but over time it was recognised as a modifiable risk for MOF. Balogh et al. identified that both primary and secondary ACS patients received significantly more fluid resuscitation (crystalloid and blood products) than patients without ACS, the average volume for secondary ACS patients was 12 l of crystalloid in the first 24 h [86]. Evolution of trauma resuscitation practices directly resulted from the research undertaken into ACS [87].

4.3.4 Shock Parameters

Base deficit (BD) and lactate have been used as indicators of shock since the 1960s [88]. BD has consistently been reported as an independent risk factor for developing MOF [8, 77, 89]. Elevated BD within the first 12 h has been shown to be a good predictor of post-injury MOF [3, 90]. MOF patients have greater levels of shock that is prolonged compared to their non-MOF counterparts with derangement of BD at 12–24 h being predictive of mortality associated with MOF [8]. A worsening BD is also a predictor of blood transfusion requirements [91].

Historically lactate was also identified as a predictor of MOF; unlike BD, it was not the baseline results that appeared predictive but higher levels at the 12–24 h mark [77] (Table 4.1).

Table 4.1 Independent predictors for MOF

ISS >25 or NISS >29 [1, 4, 77, 79, 92]
RBC >6 units [58, 77, 92, 93]
Age >55 years [77, 94]
Traumatic brain injury [4, 94, 95]
Thrombocytopenia [95–97]
BD <8 mEq/L [92, 96]
Lactate >2.5 mmol/L 12–24 h [77]
Age of blood [60]
Obesity [15, 16, 98]
ACS [85, 86]
Admission platelet count [2]
24 h maximum creatinine [2]
Male gender [99]
FFP [8, 56, 100]
Serum IL-6 levels on Day 1 [101]
Creatinine >1.8 mg/dL [102] or >150 × 10^9/L [2]

References

1. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. A 12-year prospective study of postinjury multiple organ failure: has anything changed? Arch Surg. 2005;140(5):432–8. discussion 8–40
2. Dewar DC, Tarrant SM, King KL, Balogh ZJ. Changes in the epidemiology and prediction of multiple-organ failure after injury. J Trauma Acute Care Surg. 2013;74(3):774–9.
3. Fröhlich M, Lefering R, Probst C, Paffrath T, Schneider MM, Maegele M, et al. Epidemiology and risk factors of multiple-organ failure after multiple trauma: an analysis of 31,154 patients from the TraumaRegister DGU. J Trauma Acute Care Surg. 2014;76(4):921–7. discussion 7-8
4. Brattström O, Granath F, Rossi P, Oldner A. Early predictors of morbidity and mortality in trauma patients treated in the intensive care unit. Acta Anaesthesiol Scand. 2010;54(8):1007–17.
5. Llompart-Pou JA, Talayero M, Homar J, Royo C. Multiorgan failure in the serious trauma patient. Med Intensiva. 2014;38(7):455–62.
6. 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. J Trauma Acute Care Surg. 2014;76(3):582–92. discussion 92–3
7. Ciesla DJ, Pracht EE, Tepas JJ 3rd, Cha JY, Langland-Orban B, Flint LM. The injured elderly: a rising tide. Surgery. 2013;154(2):291–8.
8. Minei JP, Cuschieri J, Sperry J, Moore EE, West MA, Harbrecht BG, et al. The changing pattern and implications of multiple organ failure after blunt injury with hemorrhagic shock. Crit Care Med. 2012;40(4):1129–35.
9. Trentzsch H, Lefering R, Nienaber U, Kraft R, Faist E, Piltz S. The role of biological sex in severely traumatized patients on outcomes: a matched-pair analysis. Ann Surg. 2015;261(4):774–80.
10. Frink M, Pape HC, van Griensven M, Krettek C, Chaudry IH, Hildebrand F. Influence of sex and age on mods and cytokines after multiple injuries. Shock. 2007;27(2):151–6.
11. Choban PS, Weireter LJ Jr, Maynes C. Obesity and increased mortality in blunt trauma. J Trauma. 1991;31(9):1253–7.
12. Neville AL, Brown CV, Weng J, Demetriades D, Velmahos GC. Obesity is an independent risk factor of mortality in severely injured blunt trauma patients. Arch Surg. 2004;139(9):983–7.
13. Bochicchio GV, Joshi M, Bochicchio K, Nehman S, Tracy JK, Scalea TM. Impact of obesity in the critically ill trauma patient: a prospective study. J Am Coll Surg. 2006;203(4):533–8.
14. Byrnes MC, McDaniel MD, Moore MB, Helmer SD, Smith RS. The effect of obesity on outcomes among injured patients. J Trauma. 2005;58(2):232–7.
15. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. Obesity increases risk of organ failure after severe trauma. J Am Coll Surg. 2006;203(4):539–45.
16. Edmonds RD, Cuschieri J, Minei JP, Rosengart MR, Maier RV, Harbrecht BG, et al. Body adipose content is independently associated with a higher risk of organ failure and nosocomial infection in the nonobese patient postinjury. J Trauma. 2011;70(2):292–8.
17. Neal MD, Cushieri J, Rosengart MR, Alarcon LH, Moore EE, Maier RV, et al. Preinjury statin use is associated with a higher risk of multiple organ failure after injury: a propensity score adjusted analysis. J Trauma. 2009;67(3):476–82. discussion 82-4
18. Harr JN, Moore EE, Johnson J, Chin TL, Wohlauer MV, Maier R, et al. Antiplatelet therapy is associated with decreased transfusion-associated risk of lung dysfunction, multiple organ failure, and mortality in trauma patients. Crit Care Med. 2013;41(2):399–404.
19. Warren HS, Elson CM, Hayden DL, Schoenfeld DA, Cobb JP, Maier RV, et al. A genomic score prognostic of outcome in trauma patients. Mol Med. 2009;15(7–8):220–7.
20. Fry DE, Pearlstein L, Fulton RL, Polk HC Jr. Multiple system organ failure. The role of uncontrolled infection. Arch Surg. 1980;115(2):136–40.
21. Artz CP, Fitts CT. Replacement therapy in shock. J Trauma. 1962;2:358–69.

22. Lewin I, Weil MH, Shubin H, Sherwin R. Pulmonary failure associated with clinical shock states. J Trauma. 1971;11(1):22–35.
23. Cotton BA, Guy JS, Morris JA Jr, Abumrad NN. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. Shock. 2006;26(2):115–21.
24. Rhee P, Wang D, Ruff P, Austin B, DeBraux S, Wolcott K, et al. Human neutrophil activation and increased adhesion by various resuscitation fluids. Crit Care Med. 2000;28(1):74–8.
25. Rhee P, Koustova E, Alam HB. Searching for the optimal resuscitation method: recommendations for the initial fluid resuscitation of combat casualties. J Trauma. 2003;54(5 Suppl):S52–62.
26. 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.
27. Balogh Z, McKinley BA, Cocanour CS, Kozar RA, Valdivia A, Sailors RM, et al. Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome. Arch Surg. 2003;138(6):637–42. discussion 42–3
28. Morrison CA, Carrick MM, Norman MA, Scott BG, Welsh FJ, Tsai P, et al. Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. J Trauma. 2011;70(3):652–63.
29. Gunter OL Jr, Au BK, Isbell JM, Mowery NT, Young PP, Cotton BA. Optimizing outcomes in damage control resuscitation: identifying blood product ratios associated with improved survival. J Trauma. 2008;65(3):527–34.
30. Evans JA, van Wessem KJ, McDougall D, Lee KA, Lyons T, Balogh ZJ. Epidemiology of traumatic deaths: comprehensive population-based assessment. World J Surg. 2010;34(1):158–63.
31. Maddock A, Corfield AR, Donald MJ, Lyon RM, Sinclair N, Fitzpatrick D, et al. Prehospital critical care is associated with increased survival in adult trauma patients in Scotland. Emerg Med J. 2020;37(3):141–5.
32. Harmsen AM, Giannakopoulos GF, Moerbeek PR, Jansma EP, Bonjer HJ, Bloemers FW. The influence of prehospital time on trauma patients outcome: a systematic review. Injury. 2015;46(4):602–9.
33. Guyette FX, Sperry JL, Peitzman AB, Billiar TR, Daley BJ, Miller RS, et al. Prehospital blood product and crystalloid resuscitation in the severely injured patient: a secondary analysis of the prehospital air medical plasma trial. Ann Surg. 2021;273(2):358–64.
34. Huβmann B, Lefering R, Taeger G, Waydhas C, Ruchholtz S. Influence of prehospital fluid resuscitation on patients with multiple injuries in hemorrhagic shock in patients from the DGU trauma registry. J Emerg Trauma Shock. 2011;4(4):465–71.
35. Lansink KW, Leenen LP. Do designated trauma systems improve outcome? Curr Opin Crit Care. 2007;13(6):686–90.
36. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967;2(7511):319–23.
37. van Wessem KJP, Leenen LPH. Incidence of acute respiratory distress syndrome and associated mortality in a polytrauma population. Trauma Surg Acute Care Open. 2018;3(1):e000232.
38. Hudson LD, Milberg JA, Anardi D, Maunder RJ. Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med. 1995;151(2 Pt 1):293–301.
39. Park PK, Cannon JW, Ye W, Blackbourne LH, Holcomb JB, Beninati W, et al. Incidence, risk factors, and mortality associated with acute respiratory distress syndrome in combat casualty care. J Trauma Acute Care Surg. 2016;81(5 Suppl 2):S150–s6. Proceedings of the 2015 Military Health System Research Symposium
40. Zielinski MD, Jenkins D, Cotton BA, Inaba K, Vercruysse G, Coimbra R, et al. Adult respiratory distress syndrome risk factors for injured patients undergoing damage-control laparotomy: AAST multicenter post hoc analysis. J Trauma Acute Care Surg. 2014;77(6):886–91.
41. Kornblith LZ, Robles AJ, Conroy AS, Redick BJ, Howard BM, Hendrickson CM, et al. Predictors of postinjury acute respiratory distress syndrome: lung injury persists in the era of hemostatic resuscitation. J Trauma Acute Care Surg. 2019;87(2):371–8.

42. Geiger EV, Lustenberger T, Wutzler S, Lefering R, Lehnert M, Walcher F, et al. Predictors of pulmonary failure following severe trauma: a trauma registry-based analysis. Scand J Trauma Resusc Emerg Med. 2013;21:34.
43. Tignanelli CJ, Hemmila MR, Rogers MAM, Raghavendran K. Nationwide cohort study of independent risk factors for acute respiratory distress syndrome after trauma. Trauma Surg Acute Care Open. 2019;4(1):e000249.
44. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. The role of the lung in postinjury multiple organ failure. Surgery. 2005;138(4):749–57. discussion 57–8
45. Regel G, Grotz M, Weltner T, Sturm JA, Tscherne H. Pattern of organ failure following severe trauma. World J Surg. 1996;20(4):422–9.
46. Villar J, Kacmarek RM, Pérez-Méndez L, Aguirre-Jaime A. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. Crit Care Med. 2006;34(5):1311–8.
47. Amato MB, Barbas CS, Medeiros DM, Magaldi RB, Schettino GP, Lorenzi-Filho G, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med. 1998;338(6):347–54.
48. Fan E, Villar J, Slutsky AS. Novel approaches to minimize ventilator-induced lung injury. BMC Med. 2013;11:85.
49. Serpa Neto A, Hemmes SN, Barbas CS, Beiderlinden M, Biehl M, Binnekade JM, et al. Protective versus conventional ventilation for surgery: a systematic review and individual patient data meta-analysis. Anesthesiology. 2015;123(1):66–78.
50. Wiersema R, Eck RJ, Haapio M, Koeze J, Poukkanen M, Keus F, et al. Burden of acute kidney injury and 90-day mortality in critically ill patients. BMC Nephrol. 2019;21(1):1.
51. Karvellas CJ, Farhat MR, Sajjad I, Mogensen SS, Leung AA, Wald R, et al. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. Crit Care. 2011;15(1):R72.
52. Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. JAMA. 2016;315(20):2190–9.
53. Duchesne JC, Kaplan LJ, Balogh ZJ, Malbrain ML. Role of permissive hypotension, hypertonic resuscitation and the global increased permeability syndrome in patients with severe hemorrhage: adjuncts to damage control resuscitation to prevent intra-abdominal hypertension. Anaesthesiol Intensive Ther. 2015;47(2):143–55.
54. Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. J Trauma. 2003;54(5):898–905. discussion −7
55. Dunne JR, Malone DL, Tracy JK, Napolitano LM. Allogenic blood transfusion in the first 24 hours after trauma is associated with increased systemic inflammatory response syndrome (SIRS) and death. Surg Infect. 2004;5(4):395–404.
56. Johnson JL, Moore EE, Kashuk JL, Banerjee A, Cothren CC, Biffl WL, et al. Effect of blood products transfusion on the development of postinjury multiple organ failure. Arch Surg. 2010;145(10):973–7.
57. Moore FA, Moore EE, Sauaia A. Blood transfusion. An independent risk factor for postinjury multiple organ failure. Arch Surg 1997;132(6):620–4; discussion 4–5.
58. Patel SV, Kidane B, Klingel M, Parry N. Risks associated with red blood cell transfusion in the trauma population, a meta-analysis. Injury. 2014;45(10):1522–33.
59. Muszynski JA, Spinella PC, Cholette JM, Acker JP, Hall MW, Juffermans NP, et al. Transfusion-related immunomodulation: review of the literature and implications for pediatric critical illness. Transfusion. 2017;57(1):195–206.
60. Zallen G, Offner PJ, Moore EE, Blackwell J, Ciesla DJ, Gabriel J, et al. Age of transfused blood is an independent risk factor for postinjury multiple organ failure. Am J Surg. 1999;178(6):570–2.
61. Gauvin F, Spinella PC, Lacroix J, Choker G, Ducruet T, Karam O, et al. Association between length of storage of transfused red blood cells and multiple organ dysfunction syndrome in pediatric intensive care patients. Transfusion. 2010;50(9):1902–13.

62. Amico F, Efird JT, Briggs GD, Lott NJ, King KL, Hirani R, et al. Association between blood donor demographics and post-injury multiple organ failure after polytrauma. Ann Surg. 2021; https://doi.org/10.1097/SLA.0000000000004754.
63. Reilly JP, Meyer NJ, Shashaty MGS, Feng R, Lanken PN, Gallop R, et al. ABO blood type a is associated with increased risk of ARDS in whites following both major trauma and severe sepsis. Chest. 2014;145(4):753–61.
64. Reilly JP, Meyer NJ, Shashaty MG, Anderson BJ, Ittner C, Dunn TG, et al. The ABO histo-blood group, endothelial activation, and acute respiratory distress syndrome risk in critical illness. J Clin Invest. 2021;131(1):e139700.
65. Cotton BA, Gunter OL, Isbell J, Au BK, Robertson AM, Morris JA Jr, et al. Damage control hematology: the impact of a trauma exsanguination protocol on survival and blood product utilization. J Trauma. 2008;64(5):1177–82. discussion 82-3
66. Stinger HK, Spinella PC, Perkins JG, Grathwohl KW, Salinas J, Martini WZ, et al. The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. J Trauma. 2008;64(2 Suppl):S79–85. discussion S
67. Murphy CH, Hess JR. Massive transfusion: red blood cell to plasma and platelet unit ratios for resuscitation of massive hemorrhage. Curr Opin Hematol. 2015;22(6):533–9.
68. O'Keeffe T, Refaai M, Tchorz K, Forestner JE, Sarode R. A massive transfusion protocol to decrease blood component use and costs. Arch Surg. 2008;143(7):686–90. discussion 90–1
69. Stein P, Kaserer A, Sprengel K, Wanner GA, Seifert B, Theusinger OM, et al. Change of transfusion and treatment paradigm in major trauma patients. Anaesthesia. 2017;72(11):1317–26.
70. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma. 2007;63(4):805–13.
71. Lim G, Harper-Kirksey K, Parekh R, Manini AF. Efficacy of a massive transfusion protocol for hemorrhagic trauma resuscitation. Am J Emerg Med. 2018;36(7):1178–81.
72. Cotton BA, Au BK, Nunez TC, Gunter OL, Robertson AM, Young PP. Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. J Trauma 2009;66(1):41–48.; discussion 8–9.
73. Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, et al. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg. 2013;148(2):127–36.
74. 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. 2015;313(5):471–82.
75. Roberts I, Shakur H, Coats T, Hunt B, Balogun E, Barnetson L, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technol Assess. 2013;17(10):1–79.
76. Balogh ZJ, Martin A, van Wessem KP, King KL, Mackay P, Havill K. Mission to eliminate postinjury abdominal compartment syndrome. Arch Surg. 2011;146(8):938–43.
77. Sauaia A, Moore FA, Moore EE, Haenel JB, Read RA, Lezotte DC. Early predictors of postinjury multiple organ failure. Arch Surg. 1994;129(1):39–45.
78. Osler T, Baker SP, Long W. A modification of the injury severity score that both improves accuracy and simplifies scoring. J Trauma. 1997;43(6):922–5. discussion 5–6
79. Balogh Z, Offner PJ, Moore EE, Biffl WL. NISS predicts postinjury multiple organ failure better than the ISS. J Trauma. 2000;48(4):624–7. discussion 7–8
80. Papavramidis TS, Marinis AD, Pliakos I, Kesisoglou I, Papavramidou N. Abdominal compartment syndrome - intra-abdominal hypertension: defining, diagnosing, and managing. J Emerg Trauma Shock. 2011;4(2):279–91.
81. Kron IL, Harman PK, Nolan SP. The measurement of intra-abdominal pressure as a criterion for abdominal re-exploration. Ann Surg. 1984;199(1):28–30.

82. Fietsam R Jr, Villalba M, Glover JL, Clark K. Intra-abdominal compartment syndrome as a complication of ruptured abdominal aortic aneurysm repair. Am Surg. 1989;55(6):396–402.
83. Kirkpatrick AW, Balogh Z, Ball CG, Ahmed N, Chun R, McBeth P, et al. The secondary abdominal compartment syndrome: iatrogenic or unavoidable? J Am Coll Surg. 2006;202(4):668–79.
84. Maxwell RA, Fabian TC, Croce MA, Davis KA. Secondary abdominal compartment syndrome: an underappreciated manifestation of severe hemorrhagic shock. J Trauma. 1999;47(6):995–9.
85. Balogh Z, McKinley BA, Cox CS Jr, Allen SJ, Cocanour CS, Kozar RA, et al. Abdominal compartment syndrome: the cause or effect of postinjury multiple organ failure. Shock. 2003;20(6):483–92.
86. Balogh Z, McKinley BA, Holcomb JB, Miller CC, Cocanour CS, Kozar RA, et al. Both primary and secondary abdominal compartment syndrome can be predicted early and are harbingers of multiple organ failure. J Trauma. 2003;54(5):848–59. discussion 59-61
87. Balogh ZJ, Lumsdaine W, Moore EE, Moore FA. Postinjury abdominal compartment syndrome: from recognition to prevention. Lancet. 2014;384(9952):1466–75.
88. Cloutier CT, Lowery BD, Carey LC. Acid-base disturbances in hemorrhagic shock. In 66 severely wounded patients prior to treatment. Arch Surg. 1969;98(5):551–7.
89. Siegel JH, Rivkind AI, Dalal S, Goodarzi S. Early physiologic predictors of injury severity and death in blunt multiple trauma. Arch Surg. 1990;125(4):498–508.
90. Sauaia A, Moore FA, Moore EE, Lezotte DC. Early risk factors for postinjury multiple organ failure. World J Surg. 1996;20(4):392–400.
91. Davis JW, Parks SN, Kaups KL, Gladen HE, O'Donnell-Nicol S. Admission base deficit predicts transfusion requirements and risk of complications. J Trauma. 1996;41(5):769–74.
92. Cryer HG, Leong K, McArthur DL, Demetriades D, Bongard FS, Fleming AW, et al. Multiple organ failure: by the time you predict it, it's already there. J Trauma. 1999;46(4):597–604. discussion −6
93. Brakenridge SC, Phelan HA, Henley SS, Golden RM, Kashner TM, Eastman AE, et al. Early blood product and crystalloid volume resuscitation: risk association with multiple organ dysfunction after severe blunt traumatic injury. J Trauma. 2011;71(2):299–305.
94. Dunham CM, Damiano AM, Wiles CE, Cushing BM. Post-traumatic multiple organ dysfunction syndrome--infection is an uncommon antecedent risk factor. Injury. 1995;26(6):373–8.
95. Eriksson J, Nelson D, Holst A, Hellgren E, Friman O, Oldner A. Temporal patterns of organ dysfunction after severe trauma. Crit Care. 2021;25(1):165.
96. Sauaia A, Moore FA, Moore EE, Norris JM, Lezotte DC, Hamman RF. Multiple organ failure can be predicted as early as 12 hours after injury. J Trauma. 1998;45(2):291–301. discussion −3
97. Nydam TL, Kashuk JL, Moore EE, Johnson JL, Burlew CC, Biffl WL, et al. Refractory postinjury thrombocytopenia is associated with multiple organ failure and adverse outcomes. J Trauma. 2011;70(2):401–6. discussion 6–7
98. Winfield RD, Delano MJ, Cuenca AG, Cendan JC, Lottenberg L, Efron PA, et al. Obese patients show a depressed cytokine profile following severe blunt injury. Shock. 2012;37(3):253–6.
99. Sperry JL, Friese RS, Frankel HL, West MA, Cuschieri J, Moore EE, et al. Male gender is associated with excessive IL-6 expression following severe injury. J Trauma. 2008;64(3):572–8. discussion 8–9
100. Watson GA, Sperry JL, Rosengart MR, Minei JP, Harbrecht BG, Moore EE, et al. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. J Trauma. 2009;67(2):221–7. discussion 8-30
101. Lausevic Z, Lausevic M, Trbojevic-Stankovic J, Krstic S, Stojimirovic B. Predicting multiple organ failure in patients with severe trauma. Can J Surg. 2008;51(2):97–102.
102. Wohlauer MV, Sauaia A, Moore EE, Burlew CC, Banerjee A, Johnson J. Acute kidney injury and posttrauma multiple organ failure: the canary in the coal mine. J Trauma Acute Care Surg. 2012;72(2):373–8. discussion 9–80

The Evolving Syndrome of Multiple Organ Failure into PICS-CCI

5

Frederick A. Moore

5.1 Introduction

Multiple organ failure (MOF) has plagued trauma intensive care units (ICUs) for more than four decades. As a result of fundamental advances in care over these decades, its epidemiology and pathobiology have evolved from being primarily a fulminant phenotype of progressive organ failure leading to early death to now a lingering phenotype of chronic critical illness (CCI) leading to frailty, long-term disabilities, and indolent death [1, 2]. In 2012, University of Florida (UF) Sepsis Critical Illness Research Center (SCIRC) coined the term *Persistent Inflammation, Immunosuppression, and Catabolism Syndrome* (PICS) to describe underlying pathobiology of this new CCI MOF phenotype that is now commonly seen in surgical ICU survivors [3]. This paradigm was proposed to provide a mechanistic framework in which to study CCI in surgical ICU patients who are now surviving previously lethal inflammatory insults (including trauma, sepsis, burns, pancreatitis, and complicated surgery). The purpose of this chapter is to describe (a) the evolving predominant phenotypes of MOF related to advances in care, (b) the emergence of PICS-CCI, and (c) the UF SCIRC ongoing efforts to validate PICS-CCI.

5.2 Evolving Predominant Phenotypes of MOF

Septic Auto-cannibalism MOF emerged in the early 1970s as a result of newly organized ICUs that allowed patients to survive single organ failure (see Fig. 5.1). Seminal reports described refractory MOF as a "fatal expression of uncontrolled infection" with a 50–80% in-hospital mortality [4]. MOF was frequently associated with intra-abdominal infection (IAI) and attention through the 1980s focused on (a)

F. A. Moore (✉)
Department of Surgery, University of Florida, Gainesville, FL, USA
e-mail: frederick.moore@surgery.ufl.edu

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_5

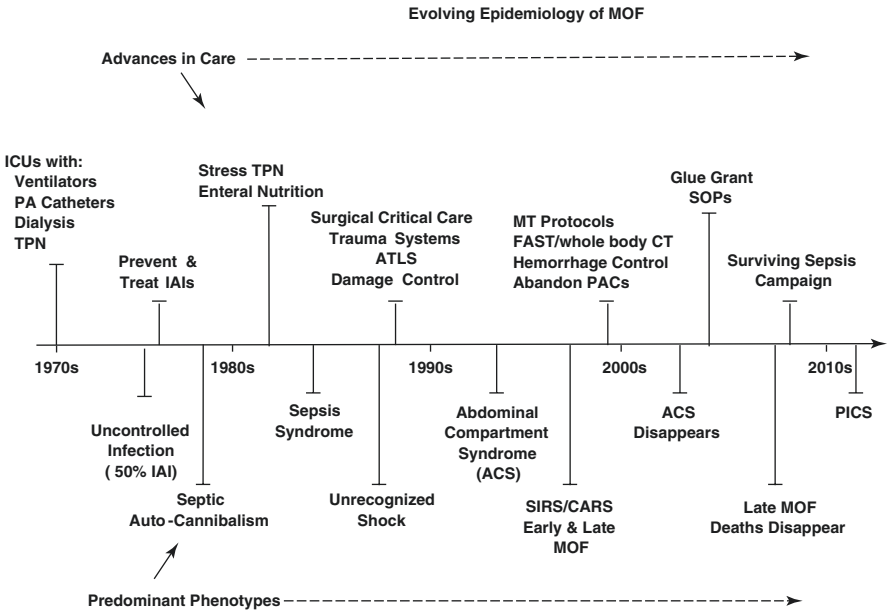


Fig. 5.1 Timeline of evolving epidemiology of multiple organ failure (MOF). *ICU* intensive care unit, *PACs* pulmonary artery catheters, *TPN* total parenteral nutrition, DO_2 oxygen delivery, *ATLS* advanced trauma life support, *SIRS* systemic inflammatory response syndrome, *CARS* compensatory anti-inflammatory response syndrome, *SOPs* standard operating procedures, *PICS* persistent, inflammation, immunosuppression, catabolism syndrome

earlier diagnosis with newly available computerized tomography (CT) scans, (b) appropriately dosing antibiotics, (c) doing better operations, and (d) developing effective percutaneous drainage. With better understanding of the injury stress response, persistent hypermetabolism was linked to immunosuppression, nosocomial infections, and worsening MOF in early survivors. In the early 1980s, the term "septic auto-cannibalism" was coined to describe this scenario and provided the rationale for the early use of stress formula total parenteral nutrition (TPN). [5] Unfortunately, early TPN in critically ill surgical patients failed to improve outcome and a series of clinical trials in the 1980s convincingly showed that early enteral nutrition (EEN) reduced nosocomial infections compared to TPN [6]. This sparked interest in role of the gut as the "motor" of MOF and at the time bacterial translocation (BT) was promulgated as an unifying explanation [7]. While the rodent studies of BT were convincing, translational human studies seriously questioned the clinical relevance of BT as an early pathologic event in MOF. Subsequent studies indicated that EEN had beneficial effects on the gut immunity which played a role reducing late nosocomial infections [8]. Most likely BT is a later pathologic event in MOF patients with ongoing gut dysfunction and disuse.

Sepsis Syndrome By the mid-1980s, it was recognized that MOF could occur without infection (e.g., blunt trauma, pancreatitis) and that both infectious and noninfectious insults caused a similar "sepsis syndrome" [1, 9]. Research refocused on determining the driving mechanism (s) of this noninfectious sepsis syndrome. At the time, new inflammatory mediators (known as "cytokines") were recognized to be produced after a variety of insults and the term "cytokine storm" was popularized [10]. Given that shock was a consistent early event, ischemia-reperfusion causing neutrophil (PMN) activation that initiated a diffuse endothelial cell injury was another attractive explanation [1]. Clinical studies showed that early MOF after major trauma could be precipitated by a massive insult or two appropriated time lesser insults [9]. Laboratory in vitro and in vivo studies characterizing PMN "priming and activation" which led the proposed "two-hit" model of MOF [11]. This was validated in in vivo rodent models of MOF and was subsequently shown to be clinically relevant in human trauma studies [12]. In the mid-1990s, the "danger hypothesis" was popularized based on the recognition that dying, necrotic, or pyroptotic cells release endogenous compounds called "damage-associated molecular patterns" (DAMPs) that acted through the same pattern recognition receptor pathways (e.g., TLR receptors) that recognize microbial products called pattern-associated molecular patterns (PAMPs) to stimulate innate immune responses [13]. This provided the mechanistic underpinnings for the role of DAMPs (including mitochondrial DNA, HMGB1, S100A, and heat shock proteins) in eliciting inflammatory responses comparable to microbial DNA, endotoxin (LPS), and proteoglycans. [14] Thus, it was widely recognized that noninfectious insults can elicit a similar sepsis syndrome which by this time was referred to as the systemic inflammatory response syndrome (SIRS).

Epidemic of the Abdominal Compartment Syndrome In the late 1980s, another enticing hypothesis was that "unrecognized shock" due to flow dependent impaired oxygen consumption caused noninfectious MOF [1]. Based on physiology, it was persuasively argued that this could be eliminated by presumptive placement of pulmonary artery catheters (PACs) in high-risk patients and pushing oxygen delivery (DO_2) to "supranormal" levels during ICU resuscitation. Based on initial compelling clinical data, this became the standard of care in many trauma ICUs [15]. Simultaneously, trauma systems, Advanced Trauma Life Support (ATLS) and "damage control" surgery were universally adopted throughout the United States. As a result of these fundamental changes in trauma care, an epidemic abdominal compartment syndrome (ACS) emerged in the mid-1990s as more severely injured patients were surviving long enough to be admitted to the ICU. Into the early 2000s, ongoing prospective studies of high-risk patients treated by standardized protocols revealed that ACS was largely an iatrogenic complication resulting from delayed hemorrhage control, overzealous ATLS crystalloid resuscitation, and futile supranormal DO_2 resuscitation in the ICU. With the widespread adoption of massive transfusion protocols, limiting early crystalloids, the FAST exam and whole body CT scans coupled with emphasis on early hemorrhage control and the abandonment PAC directed ICU resuscitation; early death from exsanguination decreased and ACS became a relatively rare event [16].

SIRS/CARS Paradigm At the same time that epidemic of ACS was occurring, "sepsis syndrome" conceptually evolved into SIRS principally mediated by PMNs that precipitated early post-injury MOF, independent of infection. However, an analysis of the Denver MOF database revealed that post-injury MOF was bimodal with 1/3rd of the cases starting early (within 72 h) while the other 2/3rd occurred later [17]. It was also recognized that SIRS was followed by delayed immune suppression [later coined the compensatory anti-inflammatory response syndrome (CARS)] [18, 19]. CARS set the stage for late infections, which, in turn, precipitated late MOF. By the late 1990s, this "SIRS/CARS" paradigm became widely accepted and the focus on ongoing research. Experimental work indicated that the production of anti-inflammatory cytokines (e.g., IL-4, IL-10) and cytokine antagonists (e.g., IL-1 receptor antagonist) were delayed and prolonged compared to the early SIRS pro-inflammatory cytokines [2]. Additionally, it was demonstrated in nonhuman primates administered live bacteria, that inhibitors of SIRS suppressed the later anti-inflammatory response. Thus, SIRS was viewed to be a pro-inflammatory "cytokine storm," whereas CARS was a compensatory anti-inflammatory cytokine response to restore immunologic homeostasis. However, as the 1990s progressed, the concept of CARS evolved to include depression in the adaptive immune response characterized to include increased lymphocyte and dendritic cell apoptosis, macrophage paralysis, elevation in regulatory T cells, decreased antigen presentation, suppressed T-cell proliferation, and a shift from type 1 helper T-cell (TH1) to TH2 lymphocyte phenotype [20].

5.3 The Emergence of PICS-CCI

The 2000 Institute on Medicine report entitled *To Err is Human* identified errors of omission to be a major cause preventable hospital deaths. Over the ensuing decade, considerable effort was directed at eliminating these errors through evidence-based guidelines (EBGs). There are two notable examples where EBG implementation dramatically improved in-hospital mortality and as a result changed the epidemiology of MOF. The first came from the "Inflammation and the Host Response to Injury" Glue Grant (GG) program funded by the National Institute of General Medical Science (NIGMS) to study the genomic response in severe blunt trauma patients and its relationship to subsequent development of MOF [21]. To reduce confounding effect of variable patient care on outcomes, the GG developed Standard Operating Procedures (SOPs) for ICU care. Over 8 years, it showed that as compliance with the SOPs improved, in-hospital mortality decreased from 22% to 11% [22]. Additionally, it was observed that while MOF continued to occur at a high rate, late MOF in-hospital deaths largely disappeared. Using high-throughput genome-wide transcriptomics, the GG made the striking observation that trauma induced a "genomic storm" with genome-wide expression of >75% of the genes [23]. Of note, this genomic storm was not consistent with the SIRS/CARS paradigm. In fact, there was simultaneous (not sequential) activation of pro-inflammatory (mediated by innate immunity) and anti-inflammatory (mediated by adaptive immunity) genes

and it was the failure this genomic storm to return to baseline gene expression that predicts non-resolution of MOF. This failure to achieve immunologic homeostasis leading prolonged ICU stays became important later (described below) when we conceptualized PICS-CCI [3].

The second notable EBG was the Surviving Sepsis Campaign (SCC) initiated in 2004 and in the following decade numerous reports documented a dramatic reduction in in-hospital mortality of severe sepsis/septic shock from >35% to <15%. In our experience in surgical sepsis, we documented a similar reduction in mortality, but made the disturbing observation that many of the survivors were not being discharged to home [24, 25]. Analysis of our sepsis database, GG trauma database, a follow-up GG validation study, and a concurrent study other surgical ICU patients (trauma, burns, pancreatitis, postoperative complications), we described the new predominant CCI phenotype of MOF upon which we based the following PICS paradigm [3, 21, 26–28]. After a major insult, a genomic storm of simultaneous pro-inflammatory SIRS and anti-inflammatory CARS can precipitate overwhelming SIRS leading to an early MOF/fulminant death trajectory. Fortunately in modern ICUs with high compliance with EBG SOPs, this fatal trajectory is markedly reduced. If patients are not allowed to die of early MOF, there are two alternatives. Most experience rapidly recovery (RAP) and are discharged to home, however in a substantial portion organ dysfunctions persist, they enter chronic critical illness (CCI). This is characterized by prolonged ICU stays with manageable organ dysfunction and ongoing inflammation (e.g., neutrophilia) that is associated with a persistent acute phase response (e.g., high CRPs and low pre-albumin levels) with ongoing protein catabolism. Despite aggressive nutritional intervention, there is a tremendous loss of lean body mass (much like cancer cachexia). They experience immunosuppression (e.g., lymphopenia) suffering recurrent nosocomial infections, poor wound healing, and decubitus ulcers. Most are discharged to long-term acute care facilities (LTACs) or skilled nursing facilities (SNFs) where they experience sepsis recidivism requiring re-hospitalization, failure to rehabilitate, and an indolent death.

5.4 Validation of PICS-CCI

Prospective Study In 2014, the UF SCIRC investigators obtained a NIGMS P50 grant to perform a five-year longitudinal cohort study to provide more definitive data. We choose to study sepsis because UF had an abundance of sepsis in their surgical and trauma ICUs. We had also established sepsis screening, diagnosis, resuscitation, and management SOPs embedded into electronic medical record (EMR) and had demonstrated high compliance with SSC EBGs that had substantially reduced mortality. [29] The purpose of the study is to define the epidemiology, dysregulated immunity, and long-term outcomes of surgical ICU patients with newly diagnosed sepsis who were treated in this standardized EBG fashion. Details of the study design as well as the clinical and laboratory SOPs utilized have been published [30]. In brief, overall cohort inclusion criteria included: (1) age ≥ 18 years;

(2) clinical diagnosis of sepsis as defined by 2001 consensus guidelines; and (3) entrance EMR based sepsis clinical management SOPs. Exclusion criteria eliminated patients whose baseline immunosuppression, end-stage comorbidities, or severe functional injuries would be a primary determinant of their long-term outcomes and thus confound outcome assessment. Clinical data was collected into an established MOF database. Blood and urine samples were collected for biomarkers at 12 h, 1, 4, 7, and 14 days, and weekly thereafter while hospitalized. Discharge disposition was classified based on known associations with long-term outcomes as either "good" (Home with or without health care services, or rehabilitation facility) or "poor" (LTAC, SNF, another acute care hospital, hospice or inpatient death). Among survivors, follow-up assessments were performed at 3, 6, and 12 months for mortality, physical function (measured by short physical performance battery), and performance status was measured by WHO/Zubrod score. Zubrod scores range is from zero to five, with increasing score reflecting worse performance status: (0) Asymptomatic and fully active; (1) Symptomatic but completely ambulatory; (2) Symptomatic with <50% in bed during the day; (3) Symptomatic with >50% in bed, but not bedbound; (4) Bedbound completely disabled and incapable of any self-care; and (5) Death. Baseline (i.e., pre-hospitalization) performance status was based upon patient/proxy reported 4-week recall assessment as soon as possible after sepsis onset.

Blood samples were analyzed in the SCIRC laboratory for biomarkers reflecting underlying pathobiology of PICS including inflammation (interleukin [IL]-6, IL-8, interferon gamma-induced protein 10 [IP-10], monocyte chemoattractant protein 1 [MCP1], granulocyte-macrophage colony-stimulating factor [GM-CSF]); stress metabolism (C-reactive protein [CRP], glucagon-like peptide 1 [GLP-1]); anabolism (insulin-like growth factor [IGF], IGF binding protein-3 [IGFBP3]); immunosuppression (soluble programmed death ligand-1 [sPDL-1] and IL-10), and angiogenesis (vascular endothelial growth factor [VEGF], soluble vascular endothelial growth factor receptor-1 [sFlt-1], angiopoietin-2 [Ang2], stromal cell-derived factor-1 [SDF-1]). Urine samples were obtained at the same time points and analyzed for evidence of catabolism (urinary 3-methyhistidine [3-MH]). Complete blood counts with differential were performed by the Clinical and Diagnostic Laboratories at the UF Health Shands Hospital. Figure 5.2 is a summary of the UF SCIRC studies that validate PICS-CCI paradigm.

Clinical Outcomes Over 4 years, 363 study patients were enrolled and followed for 1 year (see Table 5.1) [31]. Roughly half were males, predominantly Caucasian, with a median age of 62 years (40% ≥ 65 years) and a median Charlson comorbidity index of 3. Primary sites of infection were abdominal (44%), pulmonary (19%), skin/soft tissue (18%), genitourinary (12%), and vascular (7%). Overall, 30% of patients presented in sepsis, 43% in severe sepsis, and 27% in septic shock and the median APACHE II score was 17. Overall 30-day mortality was 9% with the primary causes of death being MOF (60%), respiratory failure (15%), and assorted other causes.

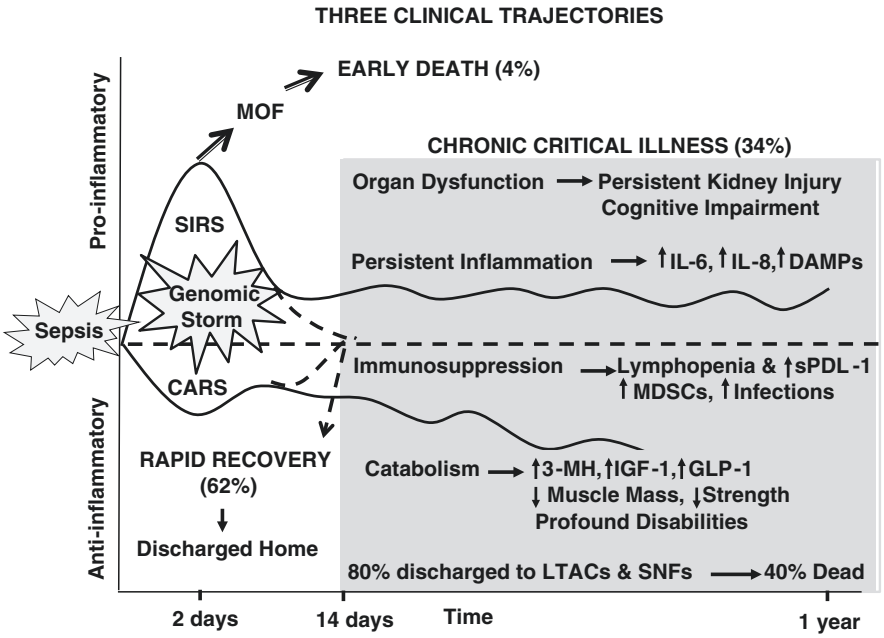


Fig. 5.2 *DAMPs* damage-associated molecular patterns, *IGF* insulin-like growth factor, *IL* interleukin, *GLP-1* glucagon-like peptide 1, *LTACs* long-term acute care facilities, *3 MH* 3 methyl histidine urinary excretion, *MDSCs* myeloid-derived suppressor cells, *SNFs* skilled nursing facilities, *sPDL-1* soluble programmed death-ligand 1

Tables 5.2 and 5.3 categorize the study patients by three predefined clinical trajectories of (1) early death, (2) RAP, and (3) CCI. Early death is defined as death within 14 days of sepsis onset. CCI is defined as an ICU stay greater than or equal to 14 days with evidence of persistent organ dysfunction based upon components of the Sequential Organ Failure Assessment (SOFA) score. RAP patients are those discharged from the ICU within 14 days with resolution of organ dysfunction. Early deaths in this surgical ICU population was surprisingly low at 4%. Additional good news was that 62% of these sepsis patients experienced RAP. However, a notably high 34% developed CCI. Not surprisingly, the CCI and RAP patients were different. The CCI patients were more likely to be male, older (mean 64 vs 58 years) and have more comorbidities. More CCI patients presented in septic shock (44% vs 15%) and as a result had higher APACHE II scores (22 vs 14). Not surprisingly, CCI patients experienced significantly more organ dysfunction (as quantified by SOFA). Of note, acute kidney injury (AKI) is surprisingly common after sepsis and was much more severe in the CCI cohort [32]. Roughly one of sepsis survivors will have persistent AKI at discharge and their mortality at 1 year is 60% [33]. CCI patients

Table 5.1 Demographics, insult characteristics, hospital outcomes and 30-day mortality of final 363 study patients

	Study patients (n = 363)
Male, *n* (%)	196 (54)
Age in years, median (25th, 75th)	62 (50, 71)
Young (≤45 years), *n* (%)	75 (21)
Middle-aged (46–64 years), *n* (%)	143 (39)
Older adults (≥65 years), *n* (%)	145 (40)
Race, *n* (%)	
Caucasian	324 (89)
African American	35 (10)
Other	4 (1)
Charlson comorbidity index, median (25th, 75th)	3 (1, 5)
Active cancer diagnosis, *n* (%)	51 (14)
Reason for hospital admission, *n* (%)	
Active infection	226 (62)
Noninfectious complication	32 (9)
Planned surgery	69 (19)
Trauma	36 (10)
Inter-facility hospital transfer, *n* (%)	152 (42)
Primary site of infection, *n* (%)	
Abdominal	160 (44)
Pulmonary	69 (19)
Skin/soft tissue	65 (18)
Genitourinary	44 (12)
Vascular	25 (7)
Sepsis severity, *n* (%)	
Sepsis	110 (30)
Severe sepsis	156 (43)
Septic shock	97 (27)
APACHE II, median (25th, 75th)	17 (11, 23)
MOF, *n* (%)	154 (42)
ICU LOS, median (25th, 75th)	7 (3, 17)
Hospital LOS, median (25th, 75th)	15 (8, 26)
30-day mortality, *n* (%)	33 (9)

also experienced more nosocomial infections (3.1 vs 1.5 per 100 hospital days) and stayed much longer in the ICU (20 vs 4 days). Most CCI patients (~80%) had a "poor" post-discharge disposition compared to most of the RAP patients (~ 80%) who had a "good" post-discharge disposition. While early mortality of the overall study population was low, the CCI cohort experienced significant ongoing post-hospital discharge mortality with a 12-month survival of only 60% (compared 95% in RAP; Fig. 5.3a). The primary causes of late CCI deaths were progressive MOF and recurrent sepsis. Unfortunately, as seen in Fig. 5.4 CCI long-term survivors had considerably worse physical function (measured by Short Physical Battery Testing), cognition (by Hopkins Verbal Learning test), and health-related quality of life (by EQ-5D-3L-Utility Index), and greater degrees of functional disability (i.e., much higher Zubrod scores) extending out at least 12 months (Fig. 5.3b) than the RAP survivors. A detailed description of these CCI versus RAP long-term outcomes in the first 173 enrolled patients can be found a recent publication [34]. In summary,

Table 5.2 Inpatient clinical trajectories and organ dysfunction of final 363 study patients

	Early death (n = 14)	CCI (n = 124)	RAP (n = 225)	p-value[a]
Male, *n* (%)	8 (57)	79 (64)	109 (48)	0.0071
Age in years, median (25th, 75th)	67 (62, 74)	64 (56, 72)	58 (45, 69)	0.0002
Charlson comorbidity index, median (25th, 75th)	4 (3, 6)	4 (2, 6)	2 (1, 4)	<0.0001
APACHE II, median (25th, 75th)	27.5 (20, 38)	22 (16, 26)	14 (10, 19)	<0.0001
Inter-facility hospital transfer, *n* (%)	9 (64)	63 (51)	80 (36)	0.4055
Septic shock, *n* (%)	10 (71)	54 (44)	33 (15)	<0.0001
MOF incidence by SOFA, *n* (%)	14 (100)	86 (69)	54 (24)	<0.0001
Maximum SOFA score, median (25th, 75th)	13.5 (12, 21)	10 (7, 13)	6 (4, 8)	<0.0001
Max. Respiratory SOFA, median (25th, 75th)	3.5 (3, 4)	3 (3, 4)	2 (2, 3)	<0.0001
Max. Cardiovascular SOFA, median (25th, 75th)	4 (1, 4)	3 (1, 3)	1 (1, 1)	<0.0001
Max. Coagulation SOFA, median (25th, 75th)	2 (1, 3)	1 (0, 2)	0 (0, 1)	<0.0001
Max. CNS SOFA, median (25th, 75th)	4 (4, 4)	3 (2.5, 4)	1 (0, 3)	<0.0001
Max. Hepatic SOFA, median (25th, 75th)	1.5 (0, 2)	0 (0, 1.5)	0 (0, 1)	0.0031
Max. Renal SOFA, median (25th, 75th)	4 (2, 4)	4 (2.5, 4)	3 (0, 4)	0.0001
Acute kidney injury, n (%)				<0.0001
KDIGO stage 1	0 (0)	35 (28)	50 (22)	
KDIGO stage 2	5 (36)	14 (11)	47 (21)	
KDIGO stage 3	9 (64)	27 (22)	13 (6)	

[a] Analysis between CCI versus RAP subjects

the P50 program has confirmed the GG observations that while MOF is still common in surgical ICUs, in-hospital MOF-related deaths are now uncommon. Roughly 1/3 of our early sepsis survivors experience the clinical trajectory is CCI which has dismal long-term outcomes.

Biomarker Studies The P50 program obtained PICS biomarkers to better understand the underlying pathobiology of the CCI patients. Figure 5.2 summarizes key observations that have been published to date. First, similar to the GG trauma studies, we have shown that sepsis induces a robust genomic response that can predict outcomes [21, 23, 28, 35]. More detailed prediction analyses including a genomic metric are ongoing in collaboration with other investigators. We also wanted to validate the concept PICS by comparing serial biomarker profiles [36–38]. It was found that the CCI cohort (versus RAP) had biomarkers reflecting: (a) persistent inflammation (increased IL-6, IL-8, MCP1, IP-10, GM-CSF), (b) immunosuppression (lymphopenia, increased sPDL-1 and IL-10), (c) persistent stress metabolism (increased CRP and GLP-1) and catabolism (increased urinary excretion 3 MH, decreased blood IGFBP3), and (d) anti-angiogenesis (decreased VEGF with increased sFlt-1, Ang2, and SDF-1). Clinical prediction models were created using

Table 5.3 Inpatient clinical trajectories and outcomes of final 363 study patients

	Early death (n = 14)	CCI (n = 124)	RAP (n = 225)	p-value[a]
Secondary infections/patient, mean (SD)	0.4 (0.5)	1 (1.1)	0.2 (0.6)	<0.0001
Secondary infections/100 hospital days, mean (SD)	5.8 (10.1)	3.1 (3.5)	1.5 (4.5)	<0.0001
ICU LOS, median (25th, 75th)	5.5 (3, 8)	20 (15, 28)	4 (2, 8)	<0.0001
Hospital LOS, median (25th, 75th)	6 (3, 10)	28 (20, 41)	10 (7, 17)	<0.0001
Discharge disposition, n (%)				<0.0001
"Good" disposition	0 (0)	27 (22)	180 (80)	<0.0001
Home	0 (0)	1 (1)	71 (31)	
Home healthcare services	0 (0)	15 (12)	94 (42)	
Rehab	0 (0)	11 (9)	15 (7)	
"Poor" disposition	14 (100)	97 (78)	45 (20)	<0.0001
Long-term acute care facility	0 (0)	50 (40)	4 (2)	
Skilled nursing facility	0 (0)	13 (10)	40 (17)	
Another hospital	0 (0)	12 (10)	1 (1)	
Hospice	1 (7)	7 (6)	0 (0)	
Death	13 (93)	15 (12)	0 (0)	

[a] Analysis between CCI versus RAP subjects

PIRO variables (predisposition, insult, response, and organ dysfunction). Biomarkers were then added to determine if they strengthened the predictions. Clinical models on day 4 accurately predicted CCI (AUC = 0.89) and on day 7 accurately predicted 1 year Zubrod 4/5 (reflecting dismal outcomes, AUC = 0.80). IL-10 and IP-10 on day 4 minimally improved prediction of CCI (AUC = 0.90). However, IL-10, IL-6, IL-8, MCP1, IP-10, Ang2, GLP-1, sPDL-1, and SDF-1 on day 7 considerably improved the prediction of 1 year Zubrod 4/5 status (AUC = 0.88). This improved prediction of 1 year Zubrod 4/5 validate that PICS plays a role underlying pathobiology of CCI and dismal long-term outcomes after sepsis.

Elderly Patients In the early 2000s, sepsis was recognized to be the "quintessential disease of the elderly" [39]. It was shown that the incidence of sepsis and in-hospital mortality increased exponentially beyond the age of 65 years [40, 41]. While age has been shown to be an independent predictor of mortality in critically ill septic patients, other important epidemiologic aspects of sepsis across age groups have not been objectively described. To further characterize the effect of age on the current epidemiology of sepsis including its long-term outcomes, we categorized our study patients by age into young (≤45 years, 20%], middle-aged (46–64 years, 40%), and older (≥65 years, 40%) patient groups [42]. Compared to young and middle-aged patients, we found that older patients had: (1) significantly more comorbidities at presentation (example chronic renal disease 6% vs 12% vs 21%), intra-abdominal infections (14% vs 25% vs 37%), septic shock (12% vs 25% vs 36%) and organ dysfunctions, (2) higher 30-day mortality (6% vs 4% vs 17%) and fewer ICU free days (median 25 vs 23 vs 20), (3) more progression into CCI (22%, vs 34% vs 42%) with higher poor disposition discharge to non-home destinations

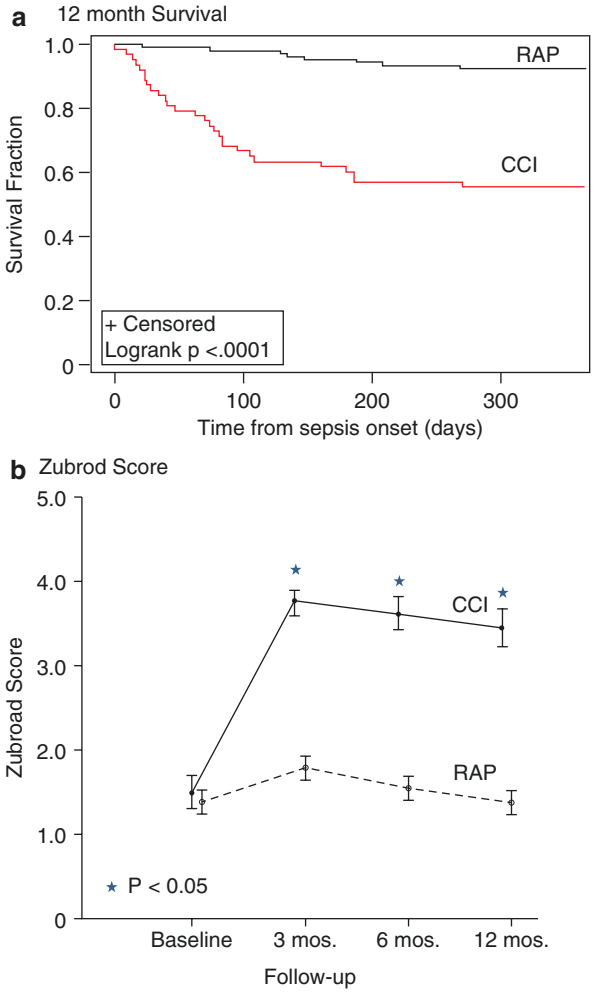


Fig. 5.3 Long-term survival and functionality in sepsis survivors. Panel A. 12 months survival in sepsis survivors who experienced CCI versus those who rapidly recovered (RAP). Panel B. Zubrod scores obtained at 3, 6, and 12 months after discharge in CCI and RAP sepsis patients

(19% vs 40% vs 62%), (4) worse 12-month mortality (11% vs 14% vs 33%), and (5) poorer Zubrod performance status and objectively measured physical and cognitive functions with only slight improvement over 12-month follow-up. We next compared serial PICS biomarkers in a) older (versus young) adults and b) older CCI (versus older RAP) patients to gain insight into underlying pathobiology of CCI in older adults. [43] We found that both the older (versus young) and older CCI (versus older RAP) patients had more persistent aberrations in biomarkers reflecting inflammation, immunosuppression, stress metabolism, catabolism, and anti-angiogenesis over 14 days after sepsis. Thus, while CCI is certainly multifactorial in elderly patients after sepsis, these data support that PICS plays a role in the underlying pathobiology.

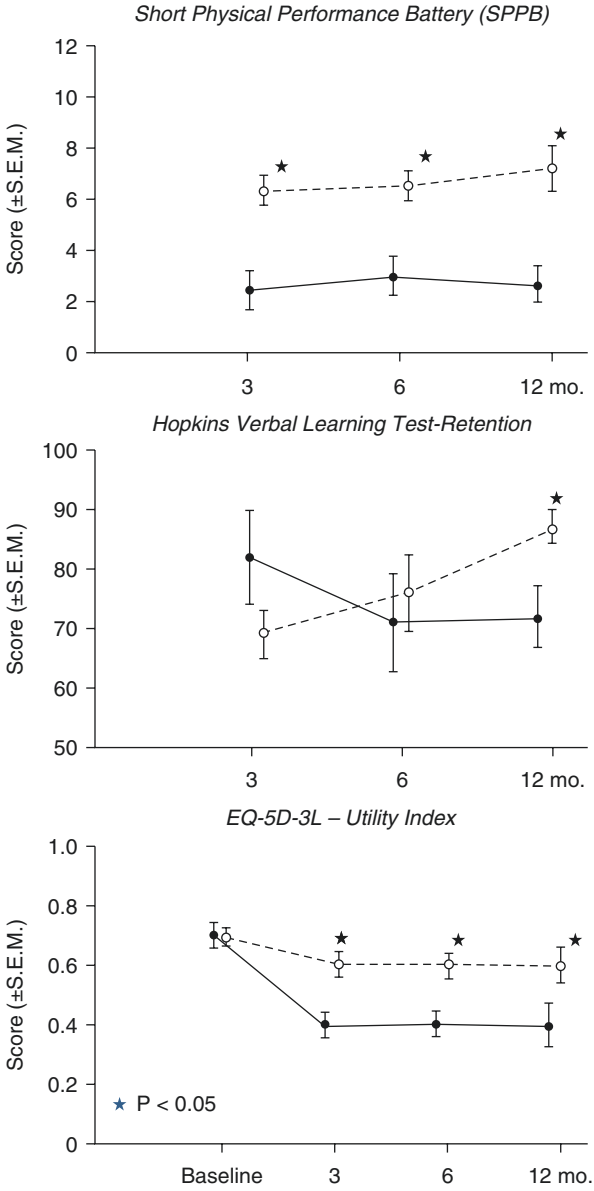


Fig. 5.4 Long-term physical function, cognition, and health-related quality of life in sepsis survivors who experience in-hospital CCI versus a rapid recovery (RAP). A higher Zubrod score indicates greater disability and a score of four indicates total chair or bed-ridden state

Translational Studies The UF SCIRC has also developed chronic murine models of sepsis and trauma to better reflect CCI-PICS and has identified the expansion of myeloid-derived suppressor cells (MDSCs) as a central mechanism for the observed immune dysregulation [44]. A focused translational study in the P50 patients confirmed the clinical relevance of these laboratory observations. It showed that the numbers of MDSCs rapidly increase after sepsis and are persistently elevated out to 28 days [45].

Moreover, MDSC expansion correlated with adverse outcomes including (a) early increased expansion was associated with early mortality, (b) persistent expansion was associated with prolonged ICU stays, and (c) persistent expansion was a strong independent predictor of nosocomial infections and poor post-discharge disposition. More interestingly, almost all the MDSCs were granulocytic with a gene expression profile reflective of a highly inflammatory and immunosuppressive transcriptome [46]. With regard to MDSC suppressor activity, MDSCs obtained prior to day 7 were not immunosuppressive, while MDSCs after day 7 suppressed T cell proliferative responses and potently suppressed stimulated T-cell production of pro-inflammatory cytokines. These data provide the theoretical basis for the use of immunostimulants that modulate MDCSs similar to what has been successfully used in advanced malignancies to achieve durable response rates. However, monotherapies will likely be ineffective and multimodality intervention will be required to interrupt the inflammation, immunosuppression, and protein catabolism that characterize PICS. Additionally, early prediction models to identify appropriate candidates and novel biomarkers to assess responses will be needed to conduct these future interventional studies.

5.5 Summary

In 2012, the UF SCIRC described how modern trauma and ICU care have largely eliminated early MOF deaths in the ICU. Unfortunately this has led to an epidemic of survivors who are progressing into new predominant CCI phenotype that has dismal long-term outcomes. Based on previous GG trauma and ongoing sepsis studies, the PICS paradigm was proposed to provide a mechanistic framework in which to study CCI in surgical ICU patients who are now surviving previously lethal inflammatory insults. The UF SCIRC obtained a NIGMS P50 program project grant and has now completed a 5-year prospective longitudinal study of 363 surgical and trauma ICU patients with new onset sepsis. These studies have shown that early deaths (< 14 days) are surprisingly low (<5%) and that the majority of study patients (>60%) rapidly recovered. However, roughly one-third progressed into CCI and ~ 80% CCI survivors had a poor post-hospital discharge disposition. It is noteworthy that at 1 year, 40% of CCI patients were dead and the remaining had persistent severe functional disabilities. Biomarker studies in these patients have: a) confirmed a robust genomic response to sepsis, b) validated the PICS paradigm using serial biomarkers that reflect persistent inflammation, immunosuppression and catabolism, c) demonstrated that the elderly (40% of study patients) are especially vulnerable to progress into the PICS-CCI trajectory, and d) confirmed that laboratory observations of MDSC expansion appear to play central role in the persistent immune dysregulation that is seen in the human CCI sepsis survivors.

Acknowledgements The research was supported in part by P50 GM111152 R01 GM104481, R01 GM113945, and T32 GM008721 grants awarded by the National Institute of General Medical Sciences. UF SCIRC collaborators Stephen D. Anton, PhD; Arza Bihorac MD, Scott C. Brakenridge, MD; Philip A. Efron, MD; Alicia M. Mohr, MD; Lyle L. Moldawer, PhD.

References

1. Moore FA, Moore EE. Evolving concepts in the pathogenesis of postinjury multiple organ failure. Surg Clin North Am. 1995;75(2):257–77.
2. Moore FA, Moore EE, Billiar TR, Vodovotz Y, Banerjee A, Moldawer LL. The role of NIGMS P50 sponsored team science in our understanding of multiple organ failure. J Trauma Acute Care surg. 2017;83(3):520–31.
3. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, Moldawer LL, Moore FA. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. 2012;72(6):1491–501.
4. Eiseman B, Beart R, Norton L. Multiple organ failure. Surg Gynecol Obstet. 1977;144(3):323–6.
5. Cerra FB, Siegel JH, Coleman B, Border JR, McMenamy RR, Septic autocannibalism. A failure of exogenous nutritional support. Ann Surg. 1980;192(4):570–80.
6. Moore FA, Feliciano DV, Andrassy RJ, McArdle AH, Booth FV, Morgenstein-Wagner TB, Kellum JM, Welling RE, Moore EE. Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis. Ann Surg. 1992;216(2):172–83.
7. Carrico CJ, Meakins JL, Marshall JC, Fry D, Maier RV. Multiple-organ-failure syndrome: the gastrointestinal tract. The "motor" of MOF. Arch Surg. 1986;121(2):196–208.
8. Hassoun HT, Kone BC, Mercer DW, Moody FG, Weisbrodt NW, Moore FA. Post-injury multiple organ failure: the role of the gut. Shock. 2001;15(1):1–10.
9. Faist E, Baue AE, Dittmer H, Heberer G. Multiple organ failure in polytrauma patients. J Trauma. 1983;23(9):775–87.
10. Dinarello CA. Historical insights into cytokines. Eur J Immunol. 2007;37(Suppl 1):S34–45.
11. Botha AJ, Moore FA, Moore EE, Fontes B, Banerjee A, Peterson VM. Postinjury neutrophil priming and activation states: therapeutic challenges. Shock. 1995;3(3):157–66.
12. Moore EE, Moore FA, Franciose RJ, Kim FJ, Biffl WL, Banerjee A. The post ischemic gut serves as a priming bed for circulating neutrophils that provoke multiple organ failure. J Trauma. 1994;37(6):881–7.
13. Matzinger P. An innate sense of danger. Semin Immunol. 1998;10(5):399–415.
14. Raymond SL, Holden DC, Mira JC, Stortz JA, Loftus TJ, Mohr AM, Moldawer LL, Moore FA. LarsonSD, Efron PA. Microbial recognition and danger signals in sepsis and trauma. Biochim Biophys Acta. 2017;1863:2564–73.
15. Moore FA, Haenel JB, Moore EE, Whitehill TA. Incommensurate oxygen consumption in response to maximal oxygen availability predicts postinjury multiple organ failure. J Trauma. 1992;33(1):58–66.
16. Balogh ZJ, Lumsdaine W, Moore EE, Moore FA. Postinjury abdominal compartment syndrome: from recognition to prevention. Lancet. 2014;384(9952):1466–75.
17. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC. Postinjury multiple organ failure: a bimodal phenomenon. J Trauma. 1996;40(4):501–10.
18. Moore FA, Peterson VM, Moore EE, Rundus C. Inadequate granulopoiesis after major torso trauma: a hematopoietic regulatory paradox. Surgery. 1990;108:667–74.
19. Bone RC. Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS). Ann Intern Med. 1996;125:680–7.
20. Mannick JA, Rodrick ML, Lederer JA. The immunologic response to injury. J Am Coll Surg. 2001;3:237–44.
21. Tompkins RG. Genomics of injury: the glue Grant experience. J Trauma Acute Care Surg. 2015;78(4):671–86.
22. Cuschieri J, Johnson JL, Sperry J, West MA, Moore EE, Minei JP, BankeyPE NAB, Cuenca AG, Efron PA, et al. Benchmarking outcomes inthe critically injured trauma patient and the effect of implementing standard operating procedures. Ann Surg. 2012;255:993–9.

23. Xiao W, Mindrinos MN, Seok J, Cuschieri J, Cuenca AG, Gao H, Hayden DL, Hennessy L, Moore EE, Minei JP, et al. A genomic storm in critically injured humans. J Exp Med. 2011;208(13):2581–90.
24. McKinley BA, Moore LJ, Sucher JF, Todd SR, Turner KL, Valdivia A, Sailors RM, Moore FA. Computer Protocol Facilitates Evidence-Based Care of Sepsis in the Surgical Intensive Care Unit. J Trauma. 2011;70(5):1153–67.
25. Moore LJ, McKinley BA, Turner KL, Todd SR, Sucher JF, Valdivia A, Sailors RM, Kao LS, Moore FA. The epidemiology of sepsis in general surgery patients. J Trauma. 2011;70(3):672–80.
26. Vanzant EL, Lopez CM, Ozrazgat-Baslanti T, Ungaro R, Davis R, Cuenca AG, Gentile LF, Nacionales DC, Cuenca AL, Bihorac A, Leeuwenburgh C, Lanz J, Baker HV, McKinley B, Moldawer LL, Moore FA, Efron PA. Persistent inflammation, immunosuppression, andcatabolism syndrome after severe blunt trauma. J Trauma Acute Care Surg. 2014;76(1):21–9.
27. Mira JC, Cuschieri J, Ozrazgat-Baslanti T, Wang Z, Ghita GL, Loftus TJ, Stortz JA, Raymond SL, Lanz JD, Hennessy LV, Brumback B, Efron PA, Baker HV, Moore FA, Maier RV, Moldawer LL, Brakenridge SC. The epidemiology of chronic critical illness after severe traumatic injury at two level-one trauma centers. Crit Care Med. 2017;45(12):1989–96.
28. Raymond SL, Hawkins RB, Wang Z, Mira JC, Stortz JA, Han F, Lanz JD, Hennessy LV, Brumback BA, Baker HV, Efron PA, Brakenridge SC, Xiao W, Tompkins RG, Cuschieri J, Moore FA, Maier RV, Moldawer LL. Prospective validation of a transcriptomic metric in severe trauma. Ann Surg. 2019; https://doi.org/10.1097/SLA.0000000000003204.
29. Croft CA, Moore FA, Efron PA, Marker PS, Gabrielli A, Westhoff LS, Lottenberg L, Jordan J, Klink V, Sailors RM, McKinley BA. Computer versus paper system for recognition and management of sepsis in surgical intensive care. J Trauma Acute Care Surg. 2014;76(2):311–9.
30. Loftus TJ, Mira JC, Ozrazgat-Baslanti T, Ghita GL, Wang Z, Stortz JA, Brumback BA, Bihorac A, Segal MS, Anton SD, Leeuwenburgh C, Mohr AM, Efron PA, Moldawer LL, Moore FA, Brakenridge SC. Sepsis and critical illness research center investigators: protocols and standard operating procedures for a prospective cohort study of sepsis in critically ill surgical patients. BMJ Open. 2017;7(7):e015136.
31. Brakenridge SC, Efron PA, Cox MC, Stortz JA, Hawkins RB, Ghita G, Gardner A, Mohr AM, Anton SD, Moldawer LL, Moore FA. Current epidemiology of surgical sepsis: discordance between inpatient mortality and 1-year outcomes. Ann Surg. 2019;270(3):502–10.
32. White LE, Hassoun HT, Bihorac A, Moore LJ, Sailors RM, McKinley BA, Valdivia A, Moore FA. Acute kidney injury is surprisingly common and a powerful predictor of mortality in surgical sepsis. J Trauma Acute Care Surg. 2013;75(3):432–8.
33. Ozrazgat-Baslanti T, Loftus TJ, Mohandas R, Wu Q, Brakenridge S, Brumback B, Efron PA, Anton S, Moore FA, Moldawer LL, Segal MS, Bihorac A. Clinical trajectories of acute kidney injury in surgical sepsis: a prospective observational study. Ann Surg. 2020; https://doi.org/10.1097/SLA.0000000000004360.
34. Gardner AK, Ghita GL, Wang Z, Ozrazgat-Baslanti T, Raymond SL, Mankowski RT, Brumback BA, Efron PA, Bihorac A, Moore FA, Anton SD, Brakenridge SC. The development of chronic critical illness determines physical function, quality of life, and long-term survival among early survivors of sepsis in surgical ICUs. Crit Care Med. 2019;47(4):566–73.
35. Sweeney TE, Perumal TM, Henao R, Nichols M, Howrylak JA, Choi AM, Bermejo-Martin JF, Almansa R, Tamayo E, Davenport EE, Burnham KL, Hinds CJ, Knight JC, Woods CW, Kingsmore SF, Ginsburg GS, Wong HR, Parnell GP, Tang B, Moldawer LL, Moore FA, Omberg L, Khatri P, Tsalik EL, Mangravite LM, Langley RJ. A community approach to mortality prediction in sepsis via gene expression analysis. Nat Commun. 2018;9(1):694.
36. Stortz JA, Mira JC, Raymond SL, Loftus TJ, Ozrazgat-Baslanti T, Wang Z, Ghita GL, Leeuwenburgh C, Segal MS, Bihorac A, Brumback BA, Mohr AM, Efron PA, Moldawer LL, Moore FA, Brakenridge SC. Benchmarking clinical outcomes and the immunocatabolic phenotype of chronic critical illness after sepsis in surgical intensive care unit patients. J Trauma Acute Care Surg. 2018;84(2):342–9.

37. Brakenridge SC, Moore FA, Mercier NR, Cox M, Wu Q, Moldawer LL, Mohr AM, Efron PA, Smith RS. Persistently elevated glucagon-like Peptide-1 levels among critically ill surgical patients after sepsis and development of chronic critical illness and dismal long-term outcomes. J Am Coll Surg. 2019;229(1):58–67.
38. Darden DB, Brakenridge SC, Efron PA, Ghita GL, Brumback B, Mohr AM, Moldawer LL, Moore FA. Biomarker evidence of the persistent inflammation, immunosuppression and catabolism syndrome (PICS) in chronic critical illness (CCI) after surgical sepsis. Ann Surg. 2021;274(4):664–73.
39. Milbrandt EB, Eldadah B, Nayfield S, Hadley E, Angus DC. Toward an integrated research agenda for critical illness in aging. Am J Respir Crit Care Med. 2010;182(8):995–1003.
40. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29(7):1303–10.
41. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. Crit Care Med. 2006;34(1):15–21.
42. Mankowski RT, Anton SD, Ghita GL, Brumback B, Cox MC, Mohr AM, Leeuwenburgh C, Moldawer LL, Efron PA, Brakenridge SC, Moore FA. Older Sepsis Survivors Suffer Persistent Disability Burden and Poor Long-Term Survival. J Am Geriatr Soc. 2020;68(9):1962–9.
43. Mankowski RT, Anton SD, Ghita GL, Brumback B, Darden DB, Bihorac A, Moldawer LL, Efron PA, Brakenridge SC, Moore FA. Older adults demonstrate biomarker evidence of the persistent inflammation, immunosuppression and catabolism syndrome (PICS) after sepsis. J Gerontol A Biol Sci Med Sci. 2021:glab080. https://doi.org/10.1093/gerona/glab080.
44. Cuenca AG, Delano MJ, Kelly-Scumpia KM, Moreno C, Scumpia PO, Laface DM, Heyworth PG, Efron PA, Moldawer LL. A paradoxical role for myeloid-derived suppressor cells in sepsis and trauma. Mol Med. 2011;17:281–92.
45. Mathias B, Delmas AL, Ozrazgat-Baslanti T, Vanzant EL, Szpila BE, Mohr AM, Moore FA, Brakenridge SC, Brumback BA, Moldawer LL, Efron PA. Human myeloid-derived suppressor cells are associated with chronic immune suppression after severe sepsis/Septic shock. Ann Surg. 2017;265(4):827–34.
46. Stortz JA, Murphy TJ, Raymond SL, Mira JC, Ungaro R, Dirain ML, Nacionales DC, Loftus TJ, Wang Z, Ozrazgat-Baslanti T, Ghita GL, Brumback BA, Mohr AM, Bihorac A, Efron PA, Moldawer LL, Moore FA, Brakenridge SC. Evidence for persistent immune suppression in patients who develop chronic critical illness after sepsis. Shock. 2018;49(3):249–58.

6 The Relevance of Traumatic Shock and Its Treatment on the Epidemiology of Multiple Organ Failure

Ayman Ali, Tommy Alan Brown II, and Juan Duchesne

6.1 Shock: Overview

Shock was first described by Hippocrates of Kos around 2400 years ago [1]. The word shock, medically speaking, is the English transliteration of the French *choquer* (to clash, offend, hurt) and was first used by the French military surgeon Henri Francois Le Dran in 1737 to describe the physiologic events that led to the death of soldiers after being shot on the battlefield [2]. More poetically, in 1872 Samuel Gross stated that shock is the "rude unhinging of the machinery of life"; and, in 1895, John Collins Warren referred to it as "a momentary pause in the act of death" [3].

In the modern, technical sense, shock is the culminating clinical manifestations of circulatory failure as a consequence of circulatory deficits and resultant decreased cellular oxygenation and tissue hypoperfusion [4]. The diagnosis of shock is based upon three criteria: clinical presentation, hemodynamics, and biochemical signs. Clinically, there are several manifestations of hypoperfusion, to include: (1) cold and clammy skin, (2) cyanosis, (3) urine output of less than 0.5 mL per kilogram of body weight per hour, and/or altered mental status. Hemodynamically, shock presents with systemic arterial hypotension defined by a systolic arterial pressure less than 90 mm Hg or mean arterial pressure less than 70 mm Hg with associated tachycardia [4]. Biochemically, it is often associated with a metabolic acidosis as a result of anaerobic metabolism leading to hyperlactatemia and a so-called base deficit [4].

A. Ali · J. Duchesne (✉)
Tulane School of Medicine, New Orleans, LA, USA
e-mail: aali5@tulane.edu; jduchesn@tulane.edu

T. A. Brown II
Harvard School of Medicine, Boston, MA, USA

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_6

6.2 Mechanisms of Shock

There are four well-established pathophysiologic mechanisms of shock: (1) hypovolemic/hemorrhagic, (2) cardiogenic, (3) obstructive, and (4) distributive. Patients can often present with a combination of the above mechanisms. For example, consider a trauma patient with a tension pneumothorax (obstructive) with a concomitant blunt cardiac injury (cardiogenic) and splenic hilar avulsion (hemorrhagic). Therefore, it is imperative to identify the etiology(ies) of a patient in shock to more accurately guide therapy as the treatment for one type of shock may have deleterious effects if given for a patient with shock due to a different cause (e.g., giving a large volume resuscitation to someone with cardiogenic shock).

Hypovolemic shock is characterized by low cardiac output, resulting in depleted intravascular volume, inadequate oxygen transport, and hypoperfusion of vital organs. This is the most common type of shock in children and is frequently seen secondary to diarrheal illnesses in developing regions [5]. Hemorrhagic shock is a subtype of the broader hypovolemic variety. It most commonly results from a traumatic injury and is the leading cause of preventable death in this population [5]. A thorough history is generally sufficient for the diagnosis of hypovolemic shock and is more sensitive and specific than the physical exam. Multiple laboratory values are typically deranged in hypovolemic shock. An elevation of BUN and creatinine secondary to prerenal kidney injury is often present. Sodium and potassium may be either elevated or depressed depending on the etiology of hypovolemia (e.g., blood loss vs. excessive emesis due to a gastric outlet obstruction). Lactic acidosis may also be present. Of note, if the source of volume loss is from the stomach patients may become alkalotic instead of acidotic [5]. Additionally, patients may present with a normal, or even elevated, hemoglobin and hematocrit secondary to a reduction in plasma volume and hemoconcentration [5].

Up to 81% of cardiogenic shock arises due to acute myocardial infarction. Cardiogenic shock may also result from inadequate cardiac contractility in cases such as end-stage cardiomyopathy, advanced valvular heart disease, myocarditis, or cardiac arrhythmias [6]. In cardiogenic shock, initial hypotension triggers a release of vasoconstrictors to re-establish normal blood pressure. However, despite the restoration of normal mean arterial blood pressure, myocardial oxygenation remains low [7]. Clinically, cardiogenic shock presents as hypotension refractory to volume resuscitation, in contrast to hypovolemic shock which is responsive to volume [8].

Obstructive shock is defined as a disorder involving impaired diastolic filling and reduced cardiac preload including vena cava compression, pulmonary embolism, cardiac tamponade, or tension pneumothorax [9]. Patho-physiologically it is classified according to the location of obstruction. It presents as a rapid, massive drop in cardiac output and blood pressure. However, unlike cardiogenic shock, the decrease in cardiac output is not related to dysfunction of the myocardium. Rather, it is related to a factor extrinsic to the heart itself. Subsequent reduced blood flow in the great vessels, or cardiac outflow with a critical drop in cardiac output, and global oxygen supply ultimately result in tissue hypoxia throughout all organ systems [9].

In distributive shock, also known as vasodilatory shock, there is a characteristic loss of regulation of vascular tone and/or disordered permeability of the vascular system [9]. The most common causes are sepsis and anaphylaxis. In sepsis, there is a massive vasodilatory response to inflammatory cytokines. A similar pathophysiologic mechanism can also be seen in patients with pancreatitis and significant burns. However, in anaphylaxis vasodilation is secondary to IgE-mediated release of histamine from mast cells and basophils [10].

In traumatic injury, the most common cause of distributive shock is neurogenic. Neurogenic shock results from injury to the spinal cord at the cervical and high thoracic levels. Shock results from autonomic dysregulation from a sudden loss of sympathetic tone with preservation of parasympathetic function [11]. The clinical manifestations of this dysregulation are hypotension with bradyarrhythmia. In the trauma patient, neurogenic shock is a diagnosis of exclusion as hemorrhagic shock is by far more common. Nonetheless, the incidence of neurogenic shock in trauma is noteworthy—approximately 19.3% in the patient with cervical cord injuries and 7% in those with thoracic injuries [12].

6.3 Approach to Shock

Although treatments to reverse of each form of shock differ (e.g., antibiotics for sepsis versus embolectomy for massive pulmonary embolism), there are general principles that guide resuscitation of the patient in shock. Most commonly is the "**VIP** rule," an approach published first in 1969 by Weil and Shubin: **V**entilate, **I**nfuse (fluids), and **P**ump (for example, vasoactive agents) [4, 13]. Despite an evolved understanding of the mechanisms of shock, and significant advances in pharmacological and mechanical techniques, these general principles have not changed much over the years.

Using the "**VIP** rule," the first step is to **V**entilate. Upon presentation with feeble or greatly labored thoracic excursion and decreased breath sounds, a clinician may reasonably suspect ventilatory failure. Measurement of pH, carbon dioxide content, and oxygen saturation on blood obtained via arterial puncture provides specific, quantitative information for identifying deficiencies in gas exchange. If respiratory acidosis is present, mechanical assistance of ventilation is usually needed. After the oxygen content of arterial blood reaches a normal level, hypoxic injury to organs and other vital tissues is reduced.

The next focus of attention is to **I**nfuse. This is of particular importance in the trauma patient with hemorrhagic shock. Fluid therapy to improve microvascular blood flow and increase cardiac output is essential. Various modalities to quantify a patient's volume status and need for repletion are currently employed. These modalities include the non-invasive (e.g., passive leg raise, 500 mL "volume challenge," and inferior vena cava diameter assessment by bedside ultrasonography) as well as more invasive techniques that require the placement of intravascular lines (e.g.,

pulse contour analysis/stroke volume variation, impedance cardiography, central venous pressure (CVP), etc.). Each of these provide a practical and near instantaneous guide for fluid repletion. If overloading the heart is of immediate concern, CVP is a reliable indication of the heart's capacity for additional volume. The third aspect in the "**VIP** rule" is the competency of the heart to serve as an effective **P**ump. In persistent severe hypotension, the use of vasopressors, typically an adrenergic agonist, is indicated.

6.4 Shock in the Intensive Care Unit

In the trauma patient, the most common form of shock is hypovolemic, specifically hemorrhagic. This differs from the medical ICU patient in which the most common form of shock is septic in nature [14]. If hemorrhagic shock is suspected, the early use of blood products over crystalloid resuscitation has been shown to result in decreased mortality and improved outcomes [5]. The preferred ratio of red cells, plasma, and platelets remains a topic of active research. Two prospective studies and a systematic review suggest a 1:1:1 transfusion ratio may reduce short-term mortality. However, this is specific to hemorrhage secondary to trauma [15–18]. In patients with hypovolemia not due to bleeding, crystalloid resuscitation is preferred over colloid [15, 19, 20].

An additional important note is that, in contrast to distributive shock (particularly septic), vasopressors are largely contraindicated. Vascular tone in hemorrhagic/hypovolemic shock is increased, and use of pressors may further reduce tissue perfusion, leading to acceleration of organ failure. Of note, an exception to this avoidance of vasopressors in hemorrhagic shock may be emerging in the form of physiologic vasopressin infusion. Recent studies have shown that autogenous vasopressin levels are diminished in hemorrhagic shock [21]. Repletion at physiologic doses appears to reduce the overall amount of transfusion required and possibly improve mortality [22].

6.5 The Epidemiology of Shock

The management of shock has changed drastically over time and there are seemingly constant advances in research and approaches. In the past few decades, there have been marked decreases in mortality with the use of aggressive, early intervention. For example, a recent temporal analysis of patients with STEMI and cardiogenic shock demonstrated a decrease in mortality from 44.6% to 33.8% over a recent 8-year period [23]. In trauma, approximately 30% of deaths are from hemorrhage, with an estimated 49,440 deaths per year in the United States alone [15]. Literature suggests that there are fewer deaths in potentially salvageable patients with the implementation of various trauma protocols, such as damage control resuscitation [24]. Other studies confirm this trend. A single center analysis showed that among patients with severe injury, mortality improved significantly over time [25] (Fig. 6.1).

Table 1. Estimated Hemorrhage-Related Deaths per Year and Years of Life Lost in the United States and Worldwide, According to the Cause of Hemorrhage.

Cause of Hemorrhage	Deaths from Hemorrhage*	U.S. Cases of Hemorrhage		Global Cases of Hemorrhage	
		No. of Deaths per Yr	Yr of Life Lost	No. of Deaths per Yr	Yr of Life Lost
	percent				
Abdominal aortic aneurysm	100	9,988†	65,273‡	191,700§	2,881,760¶
Maternal disorder	23§	138‖	7,572**	69,690‖	4,298,240**
Peptic ulcer disease	60††	1,860‖	38,597**	141,000‖	3,903,600**
Trauma	30‡‡	49,440‖	1,931,786**	1,481,700‖	74,568,000**
Total		61,426	2,043,228	1,884,090	85,651,600

* This column lists the best estimates of deaths from hemorrhage as a percentage of all deaths from the given diagnosis (e.g., all deaths from abdominal aortic aneurysm are ultimately related to hemorrhage).
† Information is from Leading Causes of Death Reports, 1981-2015, Centers for Disease Control and Prevention, 2017 (https://webappa.cdc.gov/sasweb/ncipc/leadcause.html).
‡ Data are from Years of Potential Life Lost (YPLL) Reports, 1999-2015, Centers for Disease Control and Prevention, 2017 (https://webappa.cdc.gov/sasweb/ncipc/ypll10.html).
§ Data are from Lozano et al.[5]
¶ Data are from Global Health Data Exchange, 2016 (http://ghdx.healthdata.org/gbd-results-tool).
‖ Data are from Global Health Estimates 2015: Global Deaths by Cause, Age, Sex, by Country and by Region, 2000-2015. World Health Organization, 2016 (www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html).
** Data are from Global Health Estimates 2015: Global Deaths by Cause, Age, Sex, by Country and by Region, 2000-2015. World Health Organization, 2016 (www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html).
†† Information is from Christensen et al.[6]
‡‡ Information is from Kauvar et al.[7]

Fig. 6.1 Deaths from Hemorrhage. From Cannon et al. [15]

6.6 Multiple Organ Failure: Overview

As previously described, the major consequence in all forms of shock is decreased perfusion to vital organs. Multiple organ failure (MOF) is the most used term for describing this clinical sequelae. The occurrence of organ failure is a considerable cause of mortality in the trauma patient. However, there is no single clinical definition of MOF. Since it was first described in 1977, there have been many scoring systems proposed, but no gold standard has yet to be established [26, 27]. Each of these scoring systems aim to predict outcomes in the trauma patient, including: mortality, length of stay, and time on mechanical ventilation. The most applied scoring systems include the Multiple Organ Dysfunction Score (MODS), Denver Postinjury Multiple Organ Failure Score, and the Sequential Organ Failure Assessment (SOFA) [27].

The MODS was developed in a two-stage process. First, a literature review that evaluated previous measures of organ dysfunction was conducted. From this a list of characteristics of the ideal descriptor for organ dysfunction was developed [27]. Second, a database of surgical admissions was split into development and validation sets and used to calibrate candidate measures of organ dysfunction against mortality. The MODS includes seven organ systems—respiratory, renal, hepatic, cardiac, hematological, neurologic, and gastrointestinal [27]. A cut-off total value greater than five has been widely used to denote MOF with the MODS [27].

The Denver score was developed by trauma experts in 1991, initially including eight organ systems [27]. In the mid-1990s, a modification was made reducing the number of systems to four—respiratory, renal, hepatic, and cardiac. This system was designed to predict outcomes for adult trauma patients with an injury severity score greater than 15 who survived more than 48 hours from injury. Each organ system is scored from zero to three, with a total score greater than three denoting post-trauma MOF. This cut-off value has been validated in prediction of trauma outcomes.

All of the other scoring systems were similarly developed and validated. Beyond prediction of outcomes, these scoring systems have been used to classify categories of MOF. This has motivated research and resulted in significant advances into understanding of the unique pathophysiology behind each subtype. Previous clinical understanding suggested that MOF presented as either early or late onset, a bimodal peak. This has been challenged with emerging research [28, 29]. Using the SOFA score as a clinical marker of MOF, prolonged MOF was identified as a common and unique clinical entity associated with worse outcomes in trauma patients. It has also been called the Persistent Immunosuppression and protein Catabolism Syndrome (PICS) [29–31]. This state is associated with higher mortality and infection rates, as well as higher rates of hepatic and renal dysfunction.

Of particular interest, a recent study describes three distinct forms of MOF based on severity and subsequent recovery [29]. Shepard et al. shows that our contemporary understanding of MOF has changed dramatically. The authors characterized MOF by respiratory, cardiovascular, and hemodynamic dysfunction, with the two former systems found to be dysfunctional in nearly all modern MOF [29]. This contrasts with prior studies in which respiratory and cardiovascular involvement accounted for approximately 50% of cases. The reason for this is likely multifactorial, but may be related to improved management, early identification, and rapid response to patients at risk of MOF as well as lung-protective strategies becoming the standard-of-care.

6.7 The Epidemiology of Multiple Organ Failure

Despite a decrease in the incidence of postinjury MOF over the past decade, there has not been shown to be an improvement in outcomes over time once it occurs [32]. One possible explanation for this trend is given by Sauaia et al., who suggest that high adherence to early resuscitation standards, such as standard operating procedures, has improved outcomes of the initial insult that may have provoked MOF, thus reducing the incidence of MOF [32]. However, adherence to these guidelines does not impact reversal of MOF, and therefore for those patients that develop MOF, outcomes have remained unchanged.

The advent of damage control resuscitation (DCR) is one of the largest innovations in the care of the traumatically injured patient and has yielded an improved overall survival rate. The DCR concept is designed to address the early coagulopathy in trauma by avoiding large crystalloid resuscitation, focusing instead on

replacement of that which was lost—whole blood (or blood products in a balanced ratio) [33]. It applies particularly to those trauma patients with hypothermia, acidosis, and/or significant coagulopathy [33]. DCR may be related to the decreased incidence of MOF in trauma. However, since DCR largely serves to prevent the development of MOF, it may not substantially impact the prognosis once a patent enters MOF. This may also help explain the epidemiological findings of the past decade mentioned above.

6.8 Multiple Organ Failure and Shock

There is an important correlation of MOF and the systemic inflammatory response syndrome (SIRS). In an observational study of 200 patients, 80.1% of those with SIRS on admission developed MOF compared to a 45.5% in patients without SIRS [34]. Therefore, the onset of MOF appears related to the massive release of acute-phase reactants, cytokine storm, and an inflammatory cascade seen in SIRS [35]. Various authors have described cascades that begin with SIRS and end with MOF. For many patients the association between SIRS and MOF may be a continuum of a single pathology [35]. Specifically, one hypothesized mechanism relates alteration of the coagulation pathway in SIRS related to IL-1 and TNF-α with widespread microvascular thrombosis, increased capillary permeability, and impaired tissue perfusion [35].

Additionally, a recent study by Dharap et al. showed that post-trauma inflammation and organ dysfunction were highly correlated. Patients with the above had an overall mortality of 19.5% [34]. Among their cohort, 78% developed SIRS and 72.5% MOF. Mortality was significantly associated with higher SIRS or MOF scores [34]. They found that over 54% of patients with severe MODS had evidence of SIRS. Only 13% of patients with MOF did not appear to have SIRS [34]. In addition, mortality in patients with both SIRS and MOF was significantly linked to increased mean SIRS and MOF scores [34].

6.9 Conclusion

Despite being described for millennia, there have been significant advances in management of shock and MOF in recent years. MOF rarely occurs in insolation and is closely related to SIRS—both of which are common in the traumatically injured patient. Epidemiological data suggests that the decreased incidence of shock and MOF may be due to the widespread implementation of standard practices of rapid intervention to help prevent the development of shock. However, the mortality of MOF remains largely unchanged. This suggests that future research should focus on interventions for the patient once MOF has occurred. As our understanding of the pathophysiological mechanisms behind MOF improves, the future of MOF treatment may progress to more targeted treatments with the goal of reduced mortality.

References

1. Adams F. The genuine works of Hippocrates: translated from the Greek with a preliminary discourse and annotations. London: Sydenham Society; 1849.
2. Le Dran HF. A treatise, or reflections drawn from practice on gunshot wounds. London: J. Clarke & Co; 1737.
3. Gross S. A system of surgery: pathological, diagnostic, therapeutic and operative. Philadelphia: Blanchard and Lea; 1859.
4. Vincent JL, De Backer D. Circulatory shock. N Engl J Med. 2013;369(18):1726–34.
5. Taghavi S, Askari R. Hypovolemic shock. Treasure Island, FL: StatPearls; 2021.
6. Harjola VP, Lassus J, Sionis A, Kober L, Tarvasmaki T, Spinar J, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. Eur J Heart Fail. 2015;17(5):501–9.
7. Kislitsina ON, Rich JD, Wilcox JE, Pham DT, Churyla A, Vorovich EB, et al. Shock - classification and pathophysiological principles of therapeutics. Curr Cardiol Rev. 2019;15(2):102–13.
8. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, et al. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. Circulation. 2017;136(16):e232–e68.
9. Standl T, Annecke T, Cascorbi I, Heller AR, Sabashnikov A, Teske W. The nomenclature, definition and distinction of types of shock. Dtsch Arztebl Int. 2018;115(45):757–68.
10. Smith N, Lopez RA, Silberman M. Distributive shock. Treasure Island, FL: StatPearls; 2021.
11. Dave S, Cho JJ. Neurogenic shock. Treasure Island, FL: StatPearls; 2021.
12. Guly HR, Bouamra O, Lecky FE, Trauma A, Research N. The incidence of neurogenic shock in patients with isolated spinal cord injury in the emergency department. Resuscitation. 2008;76(1):57–62.
13. Weil MH, Shubin H. The "VIP" approach to the bedside management of shock. JAMA. 1969;207(2):337–40.
14. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43(3):304–77.
15. Cannon JW. Hemorrhagic shock. N Engl J Med. 2018;378(4):370–9.
16. Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, et al. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg. 2013;148(2):127–36.
17. 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. 2015;313(5):471–82.
18. Cannon JW, Khan MA, Raja AS, Cohen MJ, Como JJ, Cotton BA, et al. Damage control resuscitation in patients with severe traumatic hemorrhage: a practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2017;82(3):605–17.
19. Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declere AD, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310(17):1809–17.
20. Marik PE, Weinmann M. Optimizing fluid therapy in shock. Curr Opin Crit Care. 2019;25(3):246–51.
21. Sims CA, Guan Y, Bergey M, Jaffe R, Holmes-Maguire L, Martin N, et al. Arginine vasopressin, copeptin, and the development of relative AVP deficiency in hemorrhagic shock. Am J Surg. 2017;214(4):589–95.
22. Sims CA, Holena D, Kim P, Pascual J, Smith B, Martin N, et al. Effect of low-dose supplementation of arginine vasopressin on need for blood product transfusions in patients with trauma and hemorrhagic shock: a randomized clinical trial. JAMA Surg. 2019;154(11):994–1003.
23. Kolte D, Khera S, Aronow WS, Mujib M, Palaniswamy C, Sule S, et al. Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. J Am Heart Assoc. 2014;3(1):e000590.

24. Langan NR, Eckert M, Martin MJ. Changing patterns of in-hospital deaths following implementation of damage control resuscitation practices in US forward military treatment facilities. JAMA Surg. 2014;149(9):904–12.
25. Dutton RP, Stansbury LG, Leone S, Kramer E, Hess JR, Scalea TM. Trauma mortality in mature trauma systems: are we doing better? An analysis of trauma mortality patterns, 1997-2008. J Trauma. 2010;69(3):620–6.
26. Eiseman B, Beart R, Norton L. Multiple organ failure. Surg Gynecol Obstet. 1977;144(3):323–6.
27. Hutchings L, Watkinson P, Young JD, Willett K. Defining multiple organ failure after major trauma: a comparison of the Denver, Sequential Organ Failure Assessment, and Marshall scoring systems. J Trauma Acute Care Surg. 2017;82(3):534–41.
28. Cole E, Gillespie S, Vulliamy P, Brohi K. Organ dysfunction in trauma study c. Multiple organ dysfunction after trauma. Br J Surg. 2020;107(4):402–12.
29. Shepherd JM, Cole E, Brohi K. Contemporary patterns of multiple organ dysfunction in trauma. Shock. 2017;47(4):429–35.
30. Minei JP, Cuschieri J, Sperry J, Moore EE, West MA, Harbrecht BG, et al. The changing pattern and implications of multiple organ failure after blunt injury with hemorrhagic shock. Crit Care Med. 2012;40(4):1129–35.
31. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. 2012;72(6):1491–501.
32. 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. J Trauma Acute Care Surg. 2014;76(3):582–92. discussion 92–3
33. Ball CG. Damage control resuscitation: history, theory and technique. Can J Surg. 2014;57(1):55–60.
34. Dharap SB, Ekhande SV. An observational study of incidence, risk factors & outcome of systemic inflammatory response & organ dysfunction following major trauma. Indian J Med Res. 2017;146(3):346–53.
35. Chakraborty RK, Burns B. Systemic inflammatory response syndrome. Treasure Island, FL: StatPearls; 2021.

Postinjury MOF with and Without Infection

7

Massimo Sartelli

7.1 Introduction

Post-trauma multiple organ failure (MOF) is the leading cause of late mortality in severe trauma, accounting for 50–60% of all deaths in such patients. Those patients that develop post-trauma MOF have generally a longer stay in the Intensive Care Unit (ICU) [1, 2].

The exact pathologic mechanism of MOF after trauma is complex and remains unexplored because of the multifactorial involvement of molecular pathways and genetic predisposition [3].

It has been proposed that the pathophysiology of MOF in trauma patients is directly associated with the alteration in the balance of the systemic inflammatory response after injury, which leads to the release of several immune mediators in the bloodstream. Secondary events, such as systemic bacterial infections, can act as a *second hit.*

7.2 Physiopathology of MOF

Although the physiopathology of MOF post severe trauma is not fully clear and has evolved over the last 30 years, it is currently accepted that the disorder is due to an alteration in the balance of the systemic inflammatory response followed by ischemia-reperfusion process after hemorrhagic shock associated to secondary events, such as a systemic bacterial infection ad post-traumatic sepsis [2].

A number of mediators and effectors can potentially intervene in the physiopathology and development of post-trauma MOF.

M. Sartelli (✉)
Department of Surgery, Macerata Hospital, Macerata, Italy

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_7

The balance between pro-inflammatory and anti-inflammatory cytokines plays a key role in the maintenance of homeostasis. Following severe trauma there is an overproduction of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, and IL-8 on the part of monocytes and macrophages. This constitutes part of the acute phase response, contributing to initiation and perpetuation of the local and systemic inflammatory response. Of the different anti-inflammatory cytokines, mention should be made of IL-10, which is synthesized by lymphocytes and monocytes and inhibits the production of TNF-α, IL-6, and IL-8 [4–7]. In trauma patients, SIRS is initiated early postinjury in response to bleeding and tissue damage, which are counteracted by a compensatory anti-inflammatory response to help restore the homeostasis. Initially, if the responses of pro- and anti-inflammatory cytokines are balanced, they may lead to the normalization of the immune response and act as a beneficial compensatory mechanism. However, if this inflammatory response remains persistent or exaggerated, it may lead to organ failure and eventually cause MOF [8, 9].

Because tissue integrity is disrupted and the immune defense system is low, trauma patients are more likely to develop infections, which may lead to sepsis and septic shock, initiating a *second hit* of post-traumatic MOF. Traumatized patients with infections have a fivefold higher mortality compared to those without infection. The overall incidence of infections following trauma varies from 9% to 36% [10]. This is much higher than the rates of nosocomial infection for general population. Ventilator-associated pneumonia (VAP) is the most frequent cause of nosocomial infection among critically ill patients requiring mechanical ventilation, with an estimated incidence of 9–27%. VAP is associated with the need for prolonged ventilatory support, ICU and hospital length of stay. Data from the National Healthcare Safety Network report showed a fourfold higher rate of VAP in intubated trauma ICU patients as compared with non-trauma cases [10]. This is likely due to the fact that trauma patients have more risk factors for VAP. These include prehospital intubation, emergency intubation, closed head and spinal cord injury, blunt chest trauma, high injury severity, and shock [10]. Early prevention of the development of sepsis following trauma can reduce the risk of both sepsis and multiple organ failure improving the patients' outcomes.

7.3 Clinical Manifestations and Assessment Scales

There is no uniform definition of post-trauma MOF. However, a number of scales have been developed for evaluating patient respiratory, cardiovascular, hepatic, renal, neurological, and coagulation function. The most widely used scale is the Sequential-related Organ Failure Assessment (SOFA).

The SOFA was developed in 1994 under the auspices of the European Society of Intensive Care Medicine as an objective tool for quantitatively assessing organ dysfunction or failure over time, and thus also for evaluating patient response to treatment [10].

The SOFA scores 6 organs. Each organ system is assigned a point value from 0 to 4 according to the degree of dysfunction in each of them. Multiorgan failure is defined as the alteration of two or more organs. Although the initial aim of the scale was to evaluate morbidity, a good correlation has been observed between the maximum score obtained and mortality. In this regard, the mortality rate is over 90% in those patients presenting a total score of over 15 (with a specificity of almost 99%) [11].

In MODS patients, cardiac, renal, and hepatic dysfunctions are generally preceded by pulmonary dysfunction.

Acute respiratory distress syndrome (ARDS) refers to an acute inflammatory response associated with diffuse lung infiltrates. In ARDS, increased permeability of the alveolar-capillary membrane causes edema and reduced oxygenation that lead to acute pulmonary heart and pulmonary hypertension in approximately 25% of patients [12].

Pulmonary vascular dysfunction in ARDS may be linked with poor prognosis. The probable importance of ventilator-induced lung injury is that apart from worsening the existing pulmonary damage it has significant systemic effects that might explain why most patients with ARDS succumb to MOF [13].

Different parameters have been associated to an increased risk of developing MOF after trauma. Those most frequently cited in the literature [13] are age, gender (previous studies had not considered the male gender to be a risk factor for the development of post-trauma MOF), severity of trauma (the severity of trauma as assessed by the Injury Severity Score (ISS) has consistently been cited as a risk), traumatic brain injury, and blood products (It is well known that blood products contain abundant mediators that act as immune modulators). As result, these parameters are associated to an increased incidence of nosocomial infections, MOF and mortality), coagulation disorders and thrombocytopenia, hemodynamic status and lactate. Other factors that have been proposed as possible predictors of the development of MOF are the minimum bilirubin levels or the peak creatinine concentrations in the first 24 h [13]. Obesity might also play a role. However, the evidence supporting these factors is much more limited.

7.4 Conclusions

Post-trauma MOF remains an important cause of morbidity-mortality in severe trauma patients. The true incidence of MOF remains unclear. The prognosis of MOF has improved in recent years, probably as a result of advances in the general management of critical trauma patients. Certain non-modifiable factors such as age and comorbidities among trauma patients imply a poorer prognosis. Early recognition allows to use protocols referred to resuscitation, damage control, sedation, and volume replacement that can mitigate their negative effects.

References

1. Sauaia A, Moore EE, Johnson JL, Chin TL, Banerjee A, Sperry JL, Maier RV, Burlew CC. Temporal trends of postinjury multiple-organ failure: still resource intensive, morbid, and lethal. J Trauma Acute Care Surg. 2014;76(3):582–92. discussion 592–3
2. Dewar D, Moore FA, Moore EE, Balogh Z. Postinjury multiple organ failure. Injury. 2009;40(9):912–8.
3. Gu C, Qiao W, Wang L, Li M, Song K. Identification of genes and pathways associated with multiple organ dysfunction syndrome by microarray analysis. Mol Med Rep. 2018;18(1):31–40.
4. Volpin G, Cohen M, Assaf M, Meir T, Katz R, Pollack S. Cytokine levels (IL-4, IL-6, IL-8 and TGFβ) as potential biomarkers of systemic inflammatory response in trauma patients. Int Orthop. 2014 Jun;38(6):1303–9.
5. Tsukamoto T, Chanthaphavong RS, Pape HC. Current theories on the pathophysiology of multiple organ failure after trauma. Injury. 2010;41(1):21–6.
6. Stahel PF, Smith WR, Moore EE. Role of biological modifiers regulating the immune response after trauma. Injury. 2007;38:1409–22.
7. Asim M, Amin F, El-Menyar A. Multiple organ dysfunction syndrome: contemporary insights on the clinicopathological spectrum. Qatar Med J. 2020;2020(1):22. https://doi.org/10.5339/qmj.2020.22.
8. Patel JC, Mollitt DL, Tepas JJ. Infectious complications in critically injured children. J Pediatr Surg. 2000;35:1174–8.
9. Pories SE, Gamelli RL, Mead PB, et al. The epidemiologic features of nosocomial infections in patients with trauma. Arch Surg. 1991;126:97–9.
10. Arumugam SK, Mudali I, Strandvik G, El-Menyar A, Al-Hassani A, Al-Thani H. Risk factors for ventilator-associated pneumonia in trauma patients: a descriptive analysis. World J Emerg Med. 2018;9(3):203–10. https://doi.org/10.5847/wjem.j.1920-8642.2018.03.007.
11. Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med. 1998;26:1793–800.
12. Osterbur K, Mann FA, Kuroki K, DeClue A. Multiple organ dysfunction syndrome in humans and animals. J Vet Intern Med. 2014;28(4):1141–51.
13. Llompart-Pou JA, Talayero M, Homar J, Royo C. Grupo de trabajo de trauma y Neurointensivismo de SEMICYUC. Multiorgan failure in the serious trauma patient. Med Intensiva. 2014;38(7):455–62.

The Relevance of the Timing of Surgical Interventions

8

Yannik Kalbas and Hans-Christoph Pape

8.1 Introduction

On arrival of a severely injured patient, it is crucial to differentiate between injuries that require immediate interventions (lifesaving procedures), those that should be done timely (Safe Definitive Surgeries [1]) and those that can be planned for a later in the reconstructive stage (e.g. maxillofacial reconstructions). Therefore, decision-making may include several processes, such as assessment of the patient, assessment of the required procedure and the perspective of management. Treating multiply injured patients requires the identification of a polytrauma patient directly on admission. The evidence-based definition of polytrauma includes a number of parameters rather than just a single one. Besides the injury pattern, five independent physiologic variables are included: hypotension, level of consciousness, acidosis, coagulopathy and age as seen in Table 8.1 [2].

Moreover, there have been several trends in nomenclature to describe treatment concepts in trauma patients (Table 8.2). These have recently been described in a standardized fashion [3].

In this line, the concept of the borderline trauma patient respects the fact that the patient status can change over time, which may affect the decision-making process. One concept that dates back to the 1990s relies on the triade of death [4]. Keel et al. suggested that patients at risk of adverse outcome, such as those with head injury, bilateral lung contusions, multiple long bone injuries, coagulopathy, hypothermia,

Y. Kalbas
Harald Tscherne Laboratory, University Hospital of Zurich, Zurich, Switzerland

Department of Trauma Surgery, University Hospital of Zurich, Zurich, Switzerland
e-mail: yannik.kalbas@usz.ch

H.-C. Pape (✉)
Department of Trauma Surgery, University Hospital of Zurich, Zurich, Switzerland
e-mail: hans-christoph.pape@usz.ch

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_8

Table 8.1 Evidence-based definition of polytrauma

AIS > 2 points and at least one of the following co-variables
• Hypotension (systolic blood pressure <90 mm Hg)
• Level of consciousness (Glasgow Coma Scale [GCS] score <8)
• Acidosis (base excess >=6.0)
• Coagulopathy (international normalized ratio 1.4/partial thromboplastin time >40 s)
• Age (>70 years)

From Pape et al. [2]

Table 8.2 Nomenclature for several concepts in trauma patients

Begriff	Indication	Injury distribution
Acute traumatic coagulopathy (ATC)	Acute haemorrhage	Undefined
Damage control resuscitation (DCR)	Acute haemorrhage	Undefined
Resuscitation associated coagulopathy (RAC)	Acute haemorrhage	Undefined
MuST-surgery: "musculoskeletal temporary surgery"	Unstable major fracture	Monotrauma
Early total care (ETC)	Unstable major fracture	Isolated or multiple fractures
Damage control orthopedics	Unstable major fracture	Multiple fractures
Early appropriate care (EAC)	Unstable major fracture	Isolated or multiple fractures
Safe definitive surgery (SDS)	Unstable major fracture	Multiple fractures

From Pfeifer et al. [3]

Table 8.3 Recommendations to consider damage control surgery within the safe definitive surgery concept

Parameter/clinical diagnosis	Recommendation
Head injury	Degree unclear in the literature, no evidence-based recommendation available
Bilateral lung contusions	TTS score [6]
Estimated operation time of >6 h	Includes visceral operations, followed by orthopaedic surgery [7]
Multiple long bone injuries	>2 of the lower extremity
Hypothermia or coagulopathy	Unresponsiveness to resuscitation

or estimated operation time of >6 h, should be considered for sequential staged surgical management [5] (Table 8.3). Other factors were added, among them the issue of soft tissue injury, which may include chest trauma, severe extremity injury or complex pelvic trauma. This lead to the definition of the borderline trauma patient, which was first summarized in 2005 and revised in 2019 (Table 8.4) [8].

For assessment of subclinical changes, inflammatory markers have been used although it is evident that the use of a single parameter is insufficient. Among multiple factors that can influence the physiological response, a solid ground continues

Table 8.4 Revised parameters to assess the borderline trauma patient in 2019

		Parameters
Static parameters	*Injury combination*	Polytrauma ISS >20 and AIS chest >2 Thoracic Trauma Score (TTS) >grade 2
	Local injury chest	Bilateral lung contusion: first plain film or Chest CT: • Unilateral bisegmental contusion • Bilateral uni- or bisegmental contusion • Flail chest
	Local injury trunc/extr	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
	Major surgery for non-lifesaving conditions	"Non-lifesaving" surgeries Flexible (day 1, 2, 3) after reassessment according to individual patient physiology: Safe definitive surgery (SDS) and damage control (DCO)
	Duration of first operative intervention	Presumed operation time >6 h Intraoperative reassessment: • Coagulopathy (ROTEM/FIBTEM) • Lactate (<2.0–2.5 mmol/L) • Body temperature stable • Requirement >3 pRBC/h
Dynamic parameters	*Blood transfusion requirements*	Massive transfusion (10 units RBCs per 6 h) Initiates "goal directed therapy" (massive transfusion protocols)
	Intra/perioperative	ROTEM/FIBTEM Lactate clearance <2.5 mmol/l (24 h)

From Pape et al. [8]

to be the triade of death (shock, hypothermia, coagulopathy) with the addition of soft tissue injuries:

1. Hypothermia is known to affect coagulation and does not address the clinical situation completely, if addressed alone [7]. It has to be viewed and treated within the general context.
2. Coagulopathy affects several other pathways, such as the cellular energy turnover and the cardiac effects induced by hypothermia. This may not allow for safe definitive surgery [9].
3. Shock causes tissue-hypoperfusion and is usually estimated by serum lactae as a marker for anearobic metabolism. However, care should be taken not to rely on lactate alone: Various metabolites may affect the measurement of metabolic acidosis [10]. Elderly with chronic diseases—such as renal failure—may demonstrate pathological lactate values [11]. These factors contribute to the general inflammatory response after trauma.
4. Soft tissue injuries of the pelvis, the extremities and the lung can further influence the course in a patient at risk and are part of the concept of borderline patients, which is summarized below.

8.2 Decision-Making: The Safe Definitive Surgery (SDS) Concept to Allow for Timely Fixation of Fractures, Including Damage Control and Early Definitive Care

After the initial assessment is completed using ATLS principles, the treating physician usually gets a fairly good impression about whether the patient is at risk for acute haemorrhage, or other problems that may lead to complications [12]. Markers of the adequacy of shock reversal, such as serum lactate, are measured routinely in trauma centres. It is undoubted that a delay of definitive surgery until the shock state is fully reversed in these cases is imperative [9].

Pursuant to this, a group in Cleveland has advocated to use acid-base changes as main parameters to assess the patient's status. They advocate that all major shaft fractures, pelvic fractures and all articular fractures should be stabilized within 72 h after injury. They base their suggestion of their Early Appropriate Care protocol on a lactate threshold level of 4 mmol/l and suggest that this should be the basis of decision-making.

This approach however, has later been questioned for several reasons. First, the lactate threshold level of 4 mmol/l being a lot higher than previously recommended in the literature. Second, the authors advocate using the first serum lactate level only. Dezman et al., from another major trauma centre in the USA, have shown however that determining the lactate clearance through serial measurements is more accurate in prediction survival after trauma. Moreover, it was found that the EAC score, like others, has never been validated. A subsequent validation revealed that the EAC protocol is less sensitive to the prediction of complications than all other scores and scales, as shown in Fig. 8.1 [13].

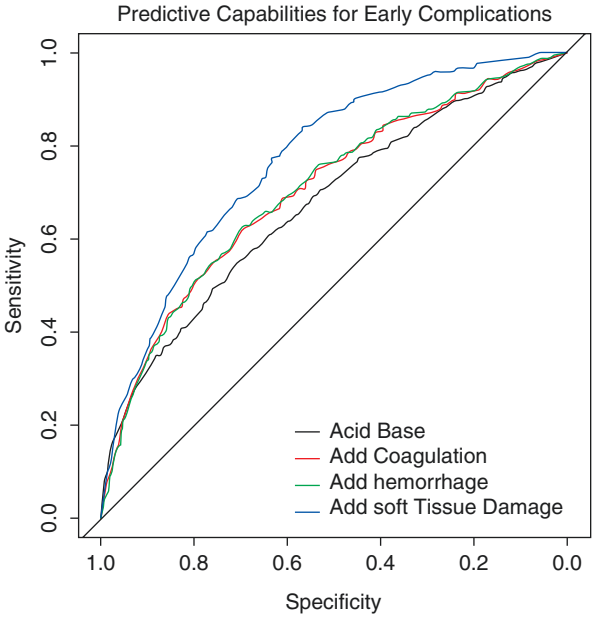
The Poly Trauma Grading Score (PTGS) was the most accurate to reconfirm that multiple parameters are important and even in a prospective data base analysis, acid-base abnormalities coagulopathy, the number of packed red blood cells (pRBCs) administered and the injury severity score have been proven to be of value [13, 14].

The *Safe Definitive Surgery* concept encompasses both, components from early definitive surgery, and damage control since the clinical scenario can change rapidly and may require a change in the management [1, 15].

While these concepts apply for the surgical approach, it is also pivotal that non-surgical causes of instability have to be addressed in a parallel fashion: This usually includes the correction of coagulopathy, hypothermia, hypovolaemia, or any combination of the four pathological cascades.

The patient's condition may range from clinically stable to a state named "in extremis", where there is imminent danger of death. Fortunately, the majority of patients belong to the group classified as "stable" or "borderline" (if stable after resuscitation) and can be safely stabilized during the course of the emergency treatment.

Stable patients have the physiological reserve to withstand prolonged operative intervention where this is appropriate and can be managed using an early total care approach, with reconstruction of complex injuries.



System	AUC	95%CI
Acid Base	0.67	0.65-0.70
Add Coagulation	0.70	0.67-0.73
Add Hemorrhage	0.71	0.68-0.73
Add Soft Tissue	0.76	0.74-0.79

Fig. 8.1 Comparison of the ability to predict early complications. The additional parameters lead to a sustained improvement in prediction of complications. Early complications include death within 72 h, death from traumatic brain injury and death from exsanguination. *AUC* area under the curve, *95% CI* 95% confidence interval. From Halvachizadeh et al. [13]

For the *borderline patient,* primary stabilization strategies may be used, but should be undertaken with caution and forethought given to operative strategy should the patient require a rapid change of treatment rationale. Additional invasive monitoring should be instituted and provision made for intensive care unit admission.

To reduce the surgical burden an unreamed nail may be considered for the femur if possible and the surgeon should be alert to the possibility of having to convert to the damage control pathway at any time throughout the procedure if the clinical condition of the patient deteriorates.

Treatment in *unstable patients* has evolved to utilize a "damage control" approach. This entails rapid lifesaving surgery only as absolutely necessitated and timely transfer to the intensive care unit for further stabilization and monitoring. Temporary stabilization of fractures using external fixation, haemorrhage control and exteriorization of gastrointestinal injuries where possible is advocated. Complex reconstructive procedures should be delayed until stability is achieved and the acute immunoinflammatory response to injury has subsided. This rationale is intended to reduce in magnitude the "second hit" of operative intervention or at least delay it until the patient is physiologically equipped to cope.

8.3 Conclusion

Decision-making should be performed rapidly and may be subject to revision before, during or after the first surgical phase. Conditions that require damage control or abbreviated surgeries may include severe head and chest trauma, multiple fractures if the patient is unstable, or uncontrollable exsanguination. Damage control orthopaedics is recommended for an unstable patient or a patient in extremis, and it has some utility for the borderline patient as well. Specific injury combinations for which damage control orthopaedics should be considered are (bilateral) femoral fractures, pelvic ring injuries with profound haemorrhage, and multiple injuries in elderly patients.

This process of decision-making may be defined as “injury-patient tailored” for damage control orthopaedics, e.g. safe definitive surgery. Regarding this strategy, it continues to be essential to validate prognostic criteria, as achieved in the polytrauma grading score. Further studies should be conducted to better understand the role of damage control orthopaedics in the treatment of patients that sustained a combination of orthopaedic trauma and concomitant injuries to the chest and head.

References

1. 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. 2015;46(1):1–3.
2. Pape HC, Lefering R, Butcher N, Peitzman A, Leenen L, Marzi I, Lichte P, Josten C, Bouillon B, Schmucker U, Stahel P, Giannoudis P, Balogh Z. 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.
3. Pfeifer R, Pape HC. Trends in nomenclature to describe concepts in trauma patients: time for standardization. Injury. 2020;51(11):2353–5.
4. Rotondo MF, Schwab CW, McGonigal MD, et al. ‘Damage control’: an approach for improved survival in exsanguinating penetrating abdominal injury. J Trauma. 1993;35(3):375–82. discussion 382–373
5. Keel M, Trentz O. Pathophysiology of polytrauma. Injury. 2005;36:691–709.
6. Pape H-C, 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.
7. Hildebrand F, Giannoudis PV, van Griensven M, Chawda M, Pape H-C. Pathophysiologic changes and effects of hypothermia on outcome in elective surgery and trauma patients. Am J Surg. 2004;187(3):363–71.
8. Pape HC, 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;50(10):1656–70.
9. 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. 2016;47(4):787–91.
10. Moviat M, Terpstra AM, Ruitenbeek W, Kluijtmans LA, Pickkers P, van der Hoeven JG. Contribution of various metabolites to the "unmeasured" anions in critically ill patients with metabolic acidosis. Crit Care Med. 2008;36:752–8.

11. Kaplan LJ, Frangos S. Clinical review: acid-base abnormalities in the intensive care unit -- part II. Crit Care. 2005;9:198–203.
12. Pape H-C, Regel G, Tscherne H. Controversies regarding early musculoskeletal management in the multiple trauma patient. Curr Opin Crit Care. 1996;2:295–303.
13. Halvachizadeh S, Baradaran L, Cinelli P, Pfeifer R, Sprengel K, Pape HC. How to detect a polytrauma patient at risk of complications: a validation and database analysis of four published scales. PLoS One. 2020;15(1):e0228082.
14. 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 Oct;46(Suppl 4):S93–8.
15. Tscherne H, Regel G, Pape H-C, Pohlemann T, Krettek C. Internal fixation of multiple fractures in patients with polytrauma. Clin Orthop Relat Res. 1998;347:62–78.

The Principles of Treatment, Modern Therapeutic Targets

9

Emiliano Gamberini, Federico Coccolini, Giovanni Scognamiglio, and Vanni Agnoletti

9.1 Introduction

Pathophysiology of Multiple Organ Failure (MOF) is driven by quite similar biochemical pathways in diverse medical, surgical and traumatic conditions [1]. Septic conditions frequently leading to MOF were extensively studied, but by the mid-1980s it was convincingly shown that organ failure can develop in the absence of infection and the concept of "generalized auto-destructive inflammation" emerged. This phenomenon became increasingly evident in severely injured patients due to our ability to keep them alive beyond the initial phases of traumatic shock.

Due to the lack of universal treatment options, MOF is global challenge for intensive care physicians.

Even with evidence-based goal-directed therapies, frequently only a single parameter is looked at during the management of an extremely complex patient. Some very aggressive goal-directed approaches like aiming for supra-normal oxygen delivery during shock resuscitation with crystalloid blouses and inotropes or strict glucose targets with insulin pumps are for the past [2].

E. Gamberini (✉)
Head of Anesthesia and Intensive Care Department, "Infermi" Hospital, Rimini, Italy

F. Coccolini
General, Emergency and Trauma Surgery Department, Surgery and Severe Trauma Division, "Cisanello" University Hospital, Pisa, Italy

G. Scognamiglio
Anesthesia and Intensive Care Department, Surgery and Severe Trauma Division, Major Trauma Center "Maurizio Bufalini" Hospital, Cesena, Italy

V. Agnoletti
Romagna Integrated Trauma System, Anesthesia and Intensive Care Department, Surgery and Severe Trauma Division, Major Trauma Center "Maurizio Bufalini" Hospital, Cesena, Italy

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_9

Generalized edema can lead to polycompartment syndrome and organ dysfunctions, which can be equally the cause or the result of MOF.

Both the theoretical and the pragmatic approach to post-injury MOF treatment should not be only a sequence of priorities, but a comprehensive approach to manage the patient (Fig. 9.1).

9.2 Analgesia and Sedation

Continuous infusion of sedative and opioid agents is generally administered to manage MOF-affected patients in the acute phase, to prevent pain, anxiety, agitation and to facilitate mechanical ventilation.

Regular reassessments for the need of sedation are daily performed by physicians in ICUs. Indications to sedate a patient are nowadays quite strict. That being said, reassessments should evaluate if a patient really needs to be sedated. If not, we need to guarantee adequate analgesia, night sleep, anxiety control, and delirium prevention or treatment, targeting our approach to a Richmond Agitation Sedation Scale (RASS) of zero or + 1 (Table 9.1). Anything over +1 can be dangerous for the

Fig. 9.1 The short blanket metaphor

Table 9.1 Richmond agitation and sedation scale (RASS)

+4	Combative	Violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious, apprehensive but movements not aggressive or vigorous
0	Alert & calm	
−1	Drowsy	Not fully alert, but has sustained awakening to *voice* (eye opening and contact ≥10 s)
−2	Light sedation	Briefly awakens to *voice* (eye opening and contact <10 s)
−3	Moderate sedation	Movement or eye opening to *voice* (but no eye contact)
−4	Deep sedation	No response to voice, but movement or eye opening to *physical* stimulation
−5	Unarousable	No response to *voice or physical* stimulation

patient. The principles of Early Comfort using Analgesia with a minimum of Sedatives and a maximum of Humanity (eCASH) summarize the modern approach to ICU sedation and analgesia [3], which are crucial in preventing medication associated iatrogenic events in an already critically ill patient (post-injury MOF).

9.2.1 Analgesia

Analgesia is usually provided by i.v. opioid continuous infusion contrary to obvious harmful side effects on intestinal motility and respiratory function in a spontaneously breathing patient. Morphine should be avoided for the risk of overdosing, especially in patients with acute renal failure. Opioid agents should be administered as the first sedative at the lowest effective dose, and multimodal analgesia should be implemented to reduce opioid consumption.

Non-opioid agents are useful in reducing opioid's dose. Systemic Acetaminophen 1 g/4–6 h, local anesthetic epidural continuous infusion, epidural clonidine 75–150 mcg/4 h, and other non-opioid drugs should be considered, if tolerated. Non-steroid analgesic drugs should be carefully considered for the increased risk of nephrotoxicity and for their intrinsic anti-platelet effect, especially in traumatic brain injury. Ketamine, an N-methyl-d-aspartate receptor antagonist, is the only available intravenous drug with simultaneous analgesic and hypnotic effects. Among sedative drugs, it has the least depressive effect on cardiovascular system. Intravenous Ketamine infusion can be combined with opioids when there is need to sedate the patient or to improve synchrony with mechanical ventilation. It is usually started with an i.v. bolus before continuous infusion. Ketamine is also useful to treat procedural pain [4].

9.2.2 Sedation

Deep sedation and analgesia are crucial parts of targeted temperature management, increased intracranial pressure, refractory status epilepticus, and severe respiratory failure. All these conditions and therapeutic modalities may also require neuromuscular blocking agents.

Continuous infusion of hypnotic drugs is inappropriately and extensively used to prevent accidental extubation and self-removal of other devices by the uncooperative yet active patient, despite the global guidelines of eCASH.

Different hypnotic agents may be suitable to different situations. Due to the frequent cardiovascular compromise in early MOF, medications with less intrinsic cardiovascular depressant effect are preferable.

Ketamine is less likely to cause hypotension than other sedatives, which makes it probably the first choice in i.v. continuous infusion until hemodynamic normalization. Combining both analgesic and sedative effects, KET may represent an alternative to other drugs for both sedation and pain control. KET can also serve as opioid-sparing agent to minimize prolonged gut dysfunction and ileus, as

demonstrated in burned patients [5, 6]. Propofol (PPF) and Dexmedetomidine (DEX) can be used as better alternatives in hemodynamically not compromised patients. Because of its short half-life, PPF is very effective when daily awake trials are scheduled, especially in severe TBI. DEX is the most recent hypnotic drug available and down-titrating infusion rate is rather easy to allow gradual shifting from deep to conscious sedation (RASS −1 to +1), minimizing the risk of delirium occurrence. Given the very limited data available, DEX cannot be recommended at the present time for daily sedation of TBI patients. Benzodiazepines (BDZ) continuous infusion should be avoided because they are more susceptible to tissue accumulation and prolong the time to awakening and confound clinical assessment. Tachyphylaxis can lead to increasingly higher doses and withdrawal symptoms may occur at drug discontinuation. BDZ have also been linked to ICU delirium [7, 8]. Long half-life BDZ may have a role in transient treatment of alcohol withdrawal syndrome.

Sleeping disorders are common in ICUs and can trigger delirium. Avoiding BDZ is a crucial part of delirium prevention together with non-pharmacologic measures to improve nighttime sleep, such as reducing noise and light, targeting mechanical ventilation to minimize respiratory efforts, limiting nursing procedures or invasive procedure execution during night shifts. Antidepressant drugs (trazodone, amitriptyline, mirtazapine), antihistamines (diphenhydramine, doxylamine) and "z-drugs" (non-benzodiazepine agonists of GABAA receptor such as zolpidem, zopiclone) are widely used to promote sleep during nighttime in ICUs. Other non-pharmacologic measures are the fist-line treatments used to manage delirium and include daily awakening trials, continuous reorientation of the patient by nursing staff, keeping clocks and calendars visible, and prompt removal of restraints and catheters. There are no double-blind, randomized, placebo-controlled trials which are adequately powered to prove the efficacy or safety of any antipsychotic agent in the management of delirium in ICU patients, although these are still commonly used by intensivists [9].

9.3 Airway Management in ICU

9.3.1 The Tracheal Tube

Most MOF patients are managed with endotracheal intubation due to the coexistence of central nervous system and respiratory failure. Orotracheal intubation (OT) is the first choice of airway management for patients needing secure airway on ICU [10]. Compared to alternatives such as nasotracheal intubation (NT) and tracheostomy (TT), OT requires deeper analgesia and sedation, which makes mouth care more difficult. The eCASH concept recommends NT or TT when hemodynamic status is improving and awake trials are to be considered.

Together with above described advantages, early TT seems to reduce Ventilator Associated Pneumonia (VAP), especially in trauma patients with severe TBI [11, 12] and it is mandatory in case of cervical Spinal Cord Injury (SCI). NT is very infrequently utilized in ICU due to the increased risk of epistaxis, sinusitis, and

VAP. These complications are likely due to the requirement for deep sedation and supine position. In some institutions, NT is getting more popular because it is superior to OT in reaching eCASH approach goals [13]. OT can be easily changed to NT by skilled physicians in awake fiberoptic nasal intubation, maintaining active mechanical ventilation and allowing transient hyperoxygenation through OT. Using pharyngeal and laryngeal local anesthesia, associated with incremental low dose analgesia and minimal sedation, an OT tube can be withdrawn when vocal cords are well visualized, and eventually a NT tube can be safely inserted through vocal cords on fiberoptic guidance. This approach is reasonable when there are no clear-cut indications for early TT and the likelihood of weaning from mechanical ventilation and extubation are high within few days. Awake fiberoptic NT during High Flow Nasal Oxygen (HFNO) could be the first choice in reintubating an ICU patient when extubation fails.

9.3.2 Bronchoalveolar Secretions Clearance and Airway Patency

Accumulation of bronchoalveolar secretions is a common problem in mechanically ventilated patients, which frequently leads to nosocomial or ventilator associated pneumonia.

Scheduled blind aspiration attempts should be discouraged because of the risk of mucosal injury.

If the patient is able to cough (RASS −1 to +1 and effective respiratory muscles), blind aspiration of the tracheal tube (avoiding to trigger cough reflex) after active cough can be enough to clear airway from secretions.

As blind aspiration should be routinely discouraged, it can only be advisable if either sudden desaturation occurs while awaiting for differential diagnosis or when ventilator flow traces suggest secretion/water in the proximal respiratory circuit. In addition to secretion, HME filters can lead to water accumulation in the circuit. Daily planned (or more frequently in patients on NMB medication) secretion clearance with flexible fiberoptic bronchoscopy is reasonable in these conditions.

Active warming and humidification must be implemented if mechanical ventilation support is expected to last more than 48 hours to facilitate secretion clearance (Fig. 9.2).

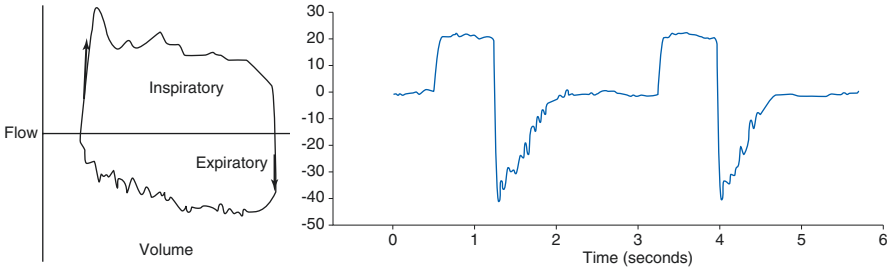


Fig. 9.2 Effect of airway secretions in flow traces on mechanical ventilators

High frequency percussive ventilation could be a viable mechanical ventilation strategy in severe hypoxemic patients when all above described procedures are ineffective, because it may also have a percussive effect that loosens thickened secretions and improves airway clearance mechanism [14].

9.4 Respiratory Failure Management and Interactions

Resuscitation with isotonic crystalloids proposed in the late 1960s contributed to a decrease in mortality and acute renal failure, but it was implicated in the emergence of Acute Respiratory Distress Syndrome (ARDS) as a major source of morbidity and mortality in ICUs.

Ischemia-reperfusion damage and direct injuries to remote organs, such as the gut, induce multiple organ dysfunctions through the release of danger signals, which are transported via the lymph from the splanchnic system to the lung and to the rest of the body. As the lung is the first organ exposed to mesenteric lymph (via the thoracic duct), this might explain the clinical observation that the lung is often the first organ to fail [1].

In addition to direct injury and secondary inflammatory-mediated damage, the lung is also subject to ventilator-induced lung injury (VILI). While mechanical ventilation (MV) is an essential therapy for respiratory failure, on the other hand MV can result in VILI that is functionally and histologically identical to that seen in ARDS.

Post-injury MOF patients usually require MV to correct hypoxemia and/or hypercarbia, to reduce the work of breathing or to surrogate spontaneous ventilation in case of procedural sedation needed for invasive and painful maneuvers.

9.4.1 Mechanical Ventilation

Contributing effects of MV to the incidence of MOF were demonstrated in the "ARDS Network lung-protective ventilation" (LPV) trial [15] and current evidence supports LPV as the standard therapy for patients at risk of ARDS [16].

Basic variables to consider a positive pressure MV as "protective" are: a Tidal Volume (Vt) of 6 ml/kg of Ideal Body Weight (IBW), an end-inspiratory Plateau Pressure (Pplat) < 30 cm H_2O, and a Driving Pressure (DP = Pplat-PEEP) < 15 cm H_2O. Even in LPV range settings, positive pressure MV induces alterations in compartments and organ functions with a direct proportional relationship to mean airway pressure [17, 18]. The protective effect on lung can be detrimental to other (frequently already compromised) organ functions.

Positive End-Expiratory Pressure (PEEP) is set to enhance alveolar volume, improving functional residual capacity through the recruitment of collapsed alveoli. Together with increasing Oxygen Inspiratory Fraction (FiO_2), PEEP can improve oxygenation in hypoxemic patients. Improvements in arterial O_2 partial pressure (PaO_2), peripheral hemoglobin oxygen saturation (SpO_2), and arterial CO_2 partial

pressure ($PaCO_2$) obtained by increasing mean airway pressure can nevertheless lead to a worse Oxygen Delivery (DO_2) (Fig. 9.3) because of MV detrimental effects on Cardiac Output (CO), overwhelming improved gas exchange (Fig. 9.4) [19]. Central venous oxygen saturation ($ScVO_2$) can be introduced as a surrogate of hemodynamic status: if both pO_2 and $ScvO_2$ increase after augmenting PEEP, it is likely that CO isn't worsened by changes of MV settings.

Judicious selection of ventilation targets (Table 9.2) and decrease of mean airway pressure according to these targets are probably the best guidance to manage MV in post-injury MOF patients. Again, eCASH and selection of sedative drugs with less depressive cardiovascular effect are a cornerstone of treatment.

This comprehensive approach to MV may decrease requirement for vasoactive drugs and i.v. fluid administration, with positive effects on both cardio-pulmonary function and intra-abdominal pressure coupled with renal function.

First choice sedative in this scenario should be KET because of no inhibitory effect on spontaneous respiratory activity, its indirect bronchodilation effect and very limited cardiovascular depressant effect [20]. Coexisting TBI has to be taken into account, because permissive hypercarbia and low arterial pH, which are

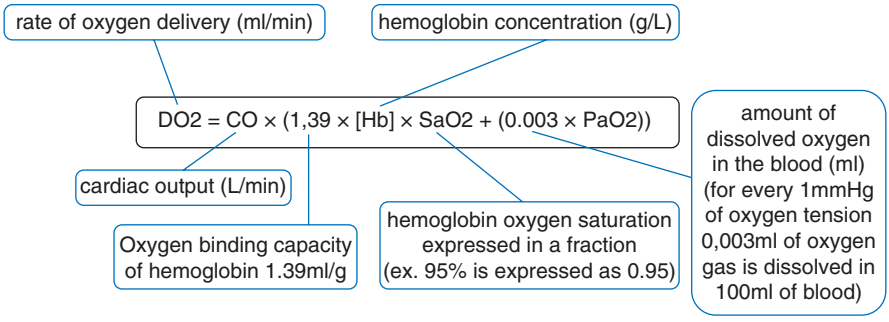


Fig. 9.3 DO_2 calculation formula

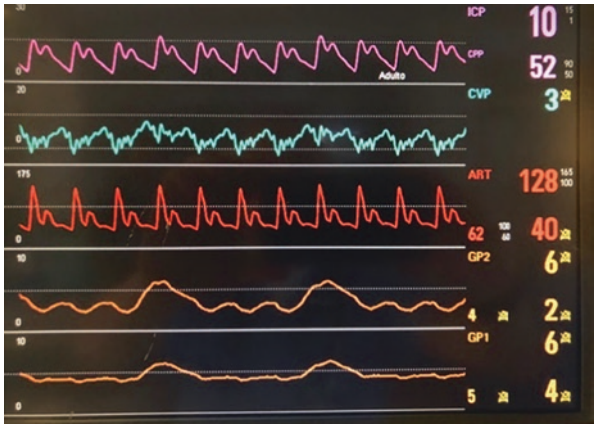


Fig. 9.4 Polycompartment continuous pressure monitoring in a multiple trauma patient with severe traumatic brain injury, bilateral pulmonary contusion, and open abdomen. *ICP* intracranial pressure, *CVP* central venous pressure, *ART* arterial pressure, *GP2* esophageal pressure, *GP1* gastric pressure

Table 9.2 Gas exchanges targets

NO severe TBI	coexisting severe TBI
pO_2 55–80 mmHg SpO_2 88–95% pCO_2 to pH > 7.20	paO_2 100 mmHg SpO_2 99% $paCO_2$ 35–40 mmHg

recommended in case of severe cardio-pulmonary failure, must be avoided for the induced cerebral arterial vasodilation and consequent ICP increase.

Pressure Support Ventilation (PSV) is an assisted spontaneous flow-cycled ventilation modality which has proved to be effective in gaining better gas exchange with lower levels of mean airway pressure. If spontaneous respiratory activity is valid, PSV should be implemented to reach both LPV range and gas exchange targets, minimizing cardiovascular interferences. Patient-Ventilator asynchrony can be difficult to deal with, particularly in flail chest affected patients and in case of pre-existing chronic respiratory failure. Neurally Adjusted Ventilation Assist (NAVA) can play an important role when fine tuning of pressure support, PEEP and expiratory trigger is ineffective in correcting asynchrony. The technique uses a special nasogastric feeding tube, which is positioned to detect diaphragm electrical activity, allowing NAVA-enabled ventilator to cycle between inspiration and expiration according to diaphragm depolarization, without any airway flow interferences [21]. Esophageal Pressure (Pes) gained recent popularity among intensivists. Continuous monitoring of Pes could help to determine if PSV should be carried on without any further risk for additional VILI. In case of excessive Pes swings, the actual ventilation strategy might not be "protective" at all. PSV can also be inadequate in cases of insufficient spontaneous breathing activity or persistent therapy persistent tachypnea. Starting or increasing KET infusion to RASS-3 to -4, even with NMB infusion, induces suppression of spontaneous breathing efforts, which allows to switch MV to passive controlled ventilation modes. Transpulmonary pressure (PL) is defined as the difference between airway pressure and Pes. In passive ventilated patients, PL allows the differentiation between chest wall and lung compliance, which redefines the concept of LPV with more meaningful monitored parameters (Table 9.3). PL can also guide the selection of the optimal PEEP value and establishing a true patient tailored ventilation. This is characterized by a PEEP just above the end-expiratory Pes based on the optimal lung compliance approach and can be beneficial in avoiding under-ventilation of patients with low chest wall compliance [22, 23].

In most severe cases, when deep sedation, controlled MV and vasoactive drugs are required, continuous Pes monitoring is recommended and frequently considered in conjunction with gastric pressure monitoring as a proxy for intra-abdominal pressure (IAP) which is normally measured via the urinary bladder.

9.4.2 Extracorporeal Respiratory Support

Veno-Venous Extracorporeal Membrane Oxygenation (VV-ECMO) has been renowned for the treatment of ARDS since 1972, in tertiary care centers capable of advanced ventilation management. Blood is withdrawn from the venous system into

Table 9.3 Lung-protective ventilation criteria

Airway pressure criteria	Transpulmonary pressure criteria
Vt = 6 ml/kg IBW PIP < 30 cmH_2O FiO_2 < 60%	ΔPL (end insp.PL-end exp.PL) <12 cm H_2O End insp.PL < 25 cm H_2O End exp.PL > 0 cm H_2O FiO_2 < 60%

an extracorporeal circuit by a mechanical pump before entering an oxygenator, and then it is returned again to the venous system.

A membrane within the oxygenator provides a blood–gas interface for gas diffusion. Recently, technological advancements in vascular cannulas, circuitry, pumps, and oxygenators have been instrumental in improving safety and promoting a wider adoption of this treatment.

According to the Extracorporeal Life Support Organization (ELSO) guidelines, the use of ECMO should be considered when the PaO_2/FiO_2 ratio is ≤150, whereas ECMO is indicated when the ratio is ≤80. A $PaCO_2$ ≥ 80 mm Hg or a Pplat≥30 cm H_2O is also considered as an indication for ECMO in patients with ARDS [24].

An anticoagulation strategy is always suggested when extracorporeal organ support is carried out: attention has to be paid in patients at high risk of re-bleeding (severe ABI, Open Abdomen, retroperitoneal hematomas, etc.). Bleeding may occur at the surgical site, at the cannula site, or into the site of a previous invasive procedure, intrathoracic, abdominal, or retroperitoneal hemorrhage may also occur. Bleeding risk is also increased by platelet dysfunction and clotting factor hemodilution. Coagulation factor consumption can be triggered by circuit clotting which requires membrane change. The need of relatively high blood flow is a contraindication to regional anticoagulation, but it is possible to reduce systemic demand for anticoagulation in the first 72 h with new heparin-coated circuits, thus diminishing VV-ECMO bleeding risk [25]. Intracerebral hemorrhage or infarction can also occur during ECMO: ICHs are sometimes related to rapid decarboxylation during VV-ECMO, whereas infarctions are more frequent during VA-ECMO due to embolism. Heparin-induced thrombocytopenia (HIT) can occur in patients receiving ECMO. When HIT is proven, heparin infusion should be stopped or replaced by a non-heparin anticoagulant. Septic complications may also result because the ECMO circuit represents a large intravascular device, and frequent manipulation increases the risk of infection.

When respiratory failure is so severe to touch the need of VV-ECMO criteria, continuous CO monitoring is mandatory.

9.5 Cardiocirculatory Support after Damage Control Resuscitation

The topic of this section is how to manage hemodynamics after an injury that caused critical bleeding and shock, when bleeding has already been stopped.

Typically this scenario starts with a sedated, intubated, mechanically ventilated and hypotensive patient, without further active bleeding and at high risk of further

complications. Hypothermia, acidosis, and acute kidney injury often coexist together with the post-resuscitation global increased permeability syndrome (GISP). Increased permeability is associated with traumatic shock and interventions aimed to improve tissue perfusion and reverse shock will produce some degree of additional tissue injury [26].

Analgesia and deep sedation with the least hemodynamic altering drugs is continued together with lung-protective mechanical ventilation.

The detailed discussion of these medications is beyond the scope of this book and also the scientific evidence on the choice of the medication is limited [2].

9.5.1 Fluid Resuscitation and De-resuscitation

While isotonic crystalloid solutions are ideal for those who have significant free water and lesser amounts of electrolyte losses, their role in the resuscitation of those with near-exsanguinating hemorrhage has been under intense investigation. Numerous studies during decades failed to demonstrate superiority of any fluid type in traumatic shock, which resulted in adherence to isotonic crystalloid solutions due to their well-known side effect profile and inexpensiveness. The Fluid and Catheter Treatment Trial (FACTT) by the ARDSNet group conducted in the post-resuscitative period demonstrated significantly fewer ventilator days in a group of critically ill patients that received less crystalloids [27].

Evaluation of fluid available options must be done with the aim of minimizing reperfusion injury instead of just on the basis of the efficacy of restoration of mean arterial pressure and similar endpoints of resuscitation.

Many researches explored predictors for fluid responsiveness and have demonstrated that it is quite easy to improve the hemodynamics after a fluid challenge. The improvement is instant but rather transient!

This cyclic resuscitation with fluid challenges results in repeatedly diminished preload (“empty heart”) but over-flooded interstitium, which further compromises tissue perfusion. Going on with zealous fluids infusion, interstitial edema will raise the pressure in all of four major body compartments: head, chest, abdomen, and extremities, and eventually the polycompartment syndrome will break through.

Treatments aimed to correct coexisting coagulation disorders must be instituted as soon as possible and continued concurrently to other procedures.

Cardiac Output monitoring is mandatory at this time, and Continuous Cardiac Output Pulmonary Artery Catheter (CCOPAC) might be superior to trans-pulmonary thermo-dilution (TPTD) in this phase (see following subsection). Guided by CCOPAC parameters, vasoactive and inotropic drugs can now be started or titrated, to get the best compromise between hemodynamics and respiratory function aiming for the best achievable DO_2.

As stated above, patients pay the price of our treatment side effects: physicians should avoid overtreatment while striving for strict oxygen/lactate/glucose/etc. values. As patient’s conditions start getting better, physicians should stop resuscitation.

Renal replacement therapy, even in absence of severe acute kidney injury, is helpful in controlling excessive fluid overload, while some fluid is inevitably given, such as nutritional support (see following subsection) and drugs. Hypertonic saline (3% and 7.4% NaCl), human albumin solution, and packed red blood cells (PRBC) are probably the best "fluid challenges" at this time, but it is difficult to postulate which one is the best option [28].

Other measures aimed to reduce GIPS duration and severity could be iv administration of high dose ascorbic acid and thiamine, high volume Continuous Veno-Venous Hemofiltration (CVVHF) or extracorporeal selective adsorption of inflammation mediators, together with stress-dose corticosteroids [29, 30].

9.5.2 Invasive Cardiac Output Monitoring

Trans-thoracic ultrasound evaluation can guide further treatment in post-injury MOF patients, but cannot be considered as a continuous monitoring tool. Continuous CO monitoring is essential in most severe MOFs, so that a bedside pulmonary and cardiac echography could guide in choosing the most appropriate method to do that.

In context with the frequently coexisting or imminent respiratory failure, transpulmonary thermo-dilution (TPTD) can be useful in managing capillary leak by providing the extravascular lung water index value and being less invasive than PAC. The limitation of this method is its accuracy in patients with left ventricle ejection fraction ≤40% or in severe depression of arterial vascular tone. This is due to the fact that continuous cardiac output is only a calculated one (not directly measured) based on the invasive arterial waveform.

When heart failure coexists, particularly with right ventricle involvement, CCOPAC can provide more accurate picture about hemodynamics from measured (instead of calculated) continuous CO, stroke volume values and with right ventricle function indexes (Right Ventricle Global End Diastolic Volume and Right Ventricle Ejection Fraction) [31].

9.5.3 Extracorporeal Cardiovascular Support

Veno-Arterial ECMO (VA-ECMO) is performed by withdrawing blood from the inferior vena cava into an extracorporeal circuit: blood is pumped by a mechanical pump through an oxygenator, and then returned into a femoral artery. In this configuration, VA-ECMO is capable to add blood flow into the descending aorta, when cardiac function remains severely depressed despite specific treatments such as inotropes and other less invasive cardiac mechanical supports. With the same harmful complication above described, VA-ECMO is more difficult to manage than VV-ECMO because the provided adjunctive blood flow is opposite to heart native blood flow, and catheterization of femoral artery with large bore cannulas often determines ipsilateral lower limb ischemia. Complications occurring during cannulation include vessel perforation with hemorrhage, arterial dissection, distal

ischemia, and incorrect location or development of pseudoaneurysm at the site of insertion.

A specific complication of VA-ECMO is the Arlequin Syndrome: fully saturated blood infused peripherally into the femoral artery from the ECMO circuit will preferentially perfuse the lower extremities and the abdominal viscera. If respiratory failure coexists, blood ejected from the heart will selectively perfuse the heart, brain, and upper extremities. As a result, cardiac and cerebral hypoxia can arise and be unrecognized if oxygenation is monitored only in the lower extremity. It is named Arlequin syndrome as upper extremity appears cyanotic while lower one appears pink. To avoid this complication, arterial oxyhemoglobin saturation should be monitored in both the upper extremity and the lower extremity. In case of Arlequin syndrome, VA-ECMO support should be discontinued if the heart seems to be recovering or a venous cannula can be implemented for VAV support.

Recent data suggests that VA-ECMO should be a salvage extreme procedure to resuscitate a patient from a refractory MOF in centers where ECMO is usually provided for other indications.

9.6 Gut Resuscitation and Nutritional Issues

About 25–30% of the entire cardiac output is directed to the gastrointestinal system. The abdominal parenchymal organs (pancreas, spleen, and liver) are making the abdominal compartment the largest blood reservoir of the entire body. During shock, splanchnic perfusion is reduced by vasoconstriction mediated by endogenous catecholamines, which is further enhanced by exogenous vasoactive drugs. The gut is the last organ to have its circulation restored after ischemia, and it is thought to play a pivotal role in the pathogenesis of post-injury MOF. Another important issue about the abdomen is the potential discrepancy between container and content, because the gut volume could increase much more than the abdominal wall could expand. It is now clear that the gut can be both a victim and an instigator of MOF, and treatment has to be set to limit this unavoidable vicious cycle. The development of abdominal compartment syndrome (ACS) can lead to polycompartment syndrome with increased intrathoracic and intracranial pressure.

9.6.1 Abdominal Organs Ischemia-Reperfusion and Intra-abdominal Pressure

Gut ischemia-reperfusion causes capillary leak and gut barrier failure. Experiments clearly demonstrated that the mesenteric lymph mediates between the gut and the systemic circulation, allowing gut-derived inflammatory mediators to reach systemic circulation [31, 32] with ongoing capillary leak creating peripheral edema, visceral organ edema and ascites in the peritoneal space. The visceral edema and ascites result in intra-abdominal hypertension (IAH) and when it is coupled with organ dysfunctions it leads to ACS (Fig. 9.4).

Aggressive fluid resuscitation and vasoactive drugs may exacerbate the capillary leak syndrome and its relationship to IAH and ACS. Limiting fluids and vasoactive drugs and early de-resuscitation strategies are measures that can prevent and even treat IAH/ACS.

Acute renal failure is frequently part of the clinical picture of ACS, and CVVHF can be an effective method to de-resuscitate the MOF patient without "stressing" the kidneys with high dose diuretic drugs.

Decompressive laparotomy is the standard method to treat severe IAH/ACS and to protect against their development in high risk situations. It has been reported to result in an immediate decrease in IAP and in improvements in organ function. Before surgical abdominal decompression, medical management can help gain some time: body positioning, nasogastric/colonic decompression, promotility agents, diuretics and continuous renal replacement therapies, NMB infusion associated with high dose KET infusion must be contemplated to reduce IAH and reverse ACS.

9.6.2 Enteral Feeding as a Specific Treatment

Early enteral nutrition (EN) is associated with decrease in infectious complications among critically ill patients, when compared to parenteral nutrition (PN) or late EN [5]. Intraluminal nutrients have been shown to reverse shock-induced mucosal hypoperfusion and restore impaired intestinal transit when given after a gut ischemia/reperfusion insult [33]. Improved transit should decrease ileus-induced bacterial colonization and translocation. Moreover, enteral nutrition attenuates the gut capillary leak that is induced by critical illness [34]. Finally and most importantly, the gut is a major immune organ and its optimal trophism is essential for immunological barrier function and ability to fight against infections.

Although there is controversy over the safety of feeding the hypoperfused small bowel of a shocked patient, evidence supports the feasibility of enteral nutrition in this setting [35].

In early shock phase, enteral infusion of glutamine counteracts the shock-induced vasoconstriction, promotes protein synthesis in the gut mucosa and protects against oxidant and cytokines induced apoptosis [36].

As shock is reversed, and if no absolute contraindications exist, EN with various enteral formulas should be instituted and progressively increased to reach nutritional goals.

9.6.3 Nutritional Goals

All trauma patients will benefit from early nutritional support, especially those who are severely injured or with pre-existing malnutrition prior to the accident. Severely injured patients are at high risk for developing a hypermetabolic state, and subsequent malnutrition. Ideal Body Wight (IBD) must be used over actual body weight in setting a proper nutritional support [37].

A caloric goal of 20–25 kcal/kg IBW/day is beneficial during the acute and initial stress response. After clinical stabilization, patients enter an anabolic recovery phase: at the present time, the aim should be to provide slightly more energy, from 25 to 30 kcal/kg IBW/day. Both predictive equations and indirect calorimetry can be used for calculating target energy goals. As for protein intake, the ASPEN/SCCM guidelines recommend 1.5–2.5/kg IBW/day, with the higher range value for obese patients [38].

With available EN formulas is often difficult to reach protein intake target without exceeding in calories, even with enteral glutamine support and particularly in obese patients, so that parenteral protein solutions usually have to be infused to get to the goal.

If EN is contraindicated or not tolerated despite prokinetic therapies, balanced PN solution should be administered.

References

1. Tsukamoto T, Chanthaphavong RS, Pape HC. Current theories on the pathophysiology of multiple organ failure after trauma. Injury. 2010;41(1):21–6. https://doi.org/10.1016/j.injury.2009.07.010.
2. Gutteling J, Girgbes ARJ. Vasoactive medications and RCT: an impossible marriage. A review and introduction the concept of enough. ICU Manag Pract. 2018;3(18):164–70.
3. Vincent JL, Shehabi Y, Walsh TS, Pandharipande PP, Ball JA, et al. Comfort and patient-centred care without excessive sedation: the eCASH concept. Intensive Care Med. 2016;42(6):962–71.
4. Devlin JW, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):e825–73. https://doi.org/10.1097/CCM.0000000000003299.
5. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. The role of the lung in postinjury multiple organ failure. Surgery. 2005;138(4):749–57.
6. Edrich T, Friedrich AD, Eltzschig HK, Felbinger TW. Ketamine for long- term sedation and analgesia of a burn patient. Anesth Analg. 2004;99(3):893–5.
7. Oddo M, Crippa IA, Mehta S, Menon D, Payen JF, Taccone FS, Citerio G. Optimizing sedation in patients with acute brain injury. Crit Care. 2016;20(1):128. https://doi.org/10.1186/s13054-016-1294-5.
8. Fraser GL, Devlin JW, Worby CP, et al. Benzodiazepine versus non- benzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. Crit Care Med. 2013;41(9 Suppl 1):S30–8.
9. Patel RP, Gambrell M, Speroff T, et al. Delirium and sedation in the intensive care unit: survey of behaviors and attitudes of 1384 healthcare professionals. Crit Care Med. 2009;37(3):825–32.
10. Dodek P, Keenan S, Cook D, Heyland D, Jacka M, Hand L, et al. Canadian critical care trials group; Canadian critical care society. Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. Ann Intern Med. 2004;141:305–13.
11. Durbin CG Jr, Perkins MP, Moores LK. Should tracheostomy be per- formed as early as 72 hours in patients requiring prolonged mechanical ventilation? Resp Care. 2010;55(1):76–87.
12. Andriolo BN, Andriolo RB, Saconato H, Atallah AN, Valente O. Early versus late tracheostomy for critically ill patients. Cochrane Database Syst Rev. 2015;1:CD007271.
13. Hariri G, Baudel JL, Dubee V, Dumas G, Joffre J, Bourcier S, Bige N, AitOufella H, Maury E. Nasotracheal intubation in ICU: an unfairly forgotten procedure. Minerva Anestesiol. 2018;84(8):997–8. https://doi.org/10.23736/S0375-9393.18.12655-1.

14. Hall JJ, Hunt JL, Arnoldo BD, Purdue GF. Use of high-frequency percussive ventilation in inhalation injuries. J Burn Care Res. 2007;28:396–400.
15. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301–8. https://doi.org/10.1056/nejm200005043421801.
16. Petrucci N, De Feo C. Lung protective ventilation strategy for the acute respiratory distress syndrome. Cochrane Database Syst Rev. 2013;2:CD003844. https://doi.org/10.1002/14651858.
17. Marini JJ, Ravenscraft SA. Mean airway pressure: physiologic determinants and clinical importance--Part 1: physiologic determinants and measurements. Crit Care Med. 1992;20(10):1461–72.
18. Marini JJ, Ravenscraft SA. Mean airway pressure: physiologic determinants and clinical importance--Part 2: clinical implications. Crit Care Med. 1992;20(11):1604–16.
19. Collino F, Rapetti F, Vasques F, Maiolo G, Tonetti T, Romitti F, Niewenhuys J, Behnemann T, Camporota L, Hahn G, Reupke V, Holke K, Herrmann P, Duscio E, Cipulli F, Moerer O, Marini JJ, Quintel M, Gattinoni L. Positive end-expiratory pressure and mechanical power. Anesthesiology. 2019;130(1):119–30. https://doi.org/10.1097/ALN.0000000000002458.
20. Jabre P, Combes X, Lapostolle F, et al. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. Lancet. 2009;374:293.
21. Patthum A, Peters M, Lockwood C. Effectiveness and safety of Neurally Adjusted Ventilatory Assist (NAVA) mechanical ventilation compared to standard conventional mechanical ventilation in optimizing patient-ventilator synchrony in critically ill patients: a systematic review protocol. JBI Database System Rev Implement Rep. 2015;13(3):31–46. https://doi.org/10.11124/jbisrir-2015-1914.
22. Akoumianaki E, Maggiore SM, Valenza F, Bellani G, Jubran A, Loring SH, Pelosi P, Talmor D, Grasso S, Chiumello D, Guérin C, Patroniti N, Ranieri VM, Gattinoni L, Nava S, Terragni PP, Pesenti A, Tobin M, Mancebo J, Brochard L. PLUG Working Group (Acute Respiratory Failure Section of the European Society of Intensive Care Medicine). The application of esophageal pressure measurement in patients with respiratory failure. Am J Respir Crit Care Med. 2014;189(5):520–31. https://doi.org/10.1164/rccm.201312-2193CI.
23. Mauri T, Yoshida T, Bellani G, Goligher EC, Carteaux G, Rittayamai N, Mojoli F, Chiumello D, Piquilloud L, Grasso S, Jubran A, Laghi F, Magder S, Pesenti A, Loring S, Gattinoni L, Talmor D, Blanch L, Amato M, Chen L, Brochard L, Mancebo J. PLeUral pressure working Group (PLUG—Acute Respiratory Failure section of the European Society of Intensive Care Medicine). Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. Intensive Care Med. 2016;42(9):1360–73. https://doi.org/10.1007/s00134-016-4400-x.
24. General Guidelines for all ECLS Cases. Extracorporeal Life Support Organization. Available at: http://www.elso.org/Portals/0/IGD/Archive/FileManager/929122ae88cusersshyerdocumentselsoguidelinesgeneralalleclsversion1.3.pdf. Accessed 4 Mar 2015.
25. Arlt M, Philipp A, Voelkel S, et al. Extracorporeal membrane oxy- genation in severe trauma patients with bleeding shock. Resuscitation. 2010;81(7):804–9.
26. Duchesne JC, Kaplan LJ, Balogh ZJ, Malbrain ML. Role of permissive hypotension, hypertonic resuscitation and the global increased permeability syndrome in patients with severe hemorrhage: adjuncts to damage control resuscitation to prevent intra-abdominal hypertension. Anaesthesiol Intens Ther. 2015;47(2):143–55. https://doi.org/10.5603/AIT.a2014.0052.
27. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid management strategies in acute lung injury. N Engl J Med. 2006;354:2564–75.
28. Cordemans C, De Laet I, Van Regenmortel N, et al. Fluid management in critically ill patients: the role of extravascular lung water, abdominal hypertension, capillary leak and fluid balance. Ann Intensive Care. 2012;2(Suppl 1):S1.
29. Vincent JL. How I treat septic shock. Intensive Care Med. 2018;44(12):2242–4. https://doi.org/10.1007/s00134-018-5401-8.

30. Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med. 2008;36(6):1937–49. https://doi.org/10.1097/ccm.0b013e31817603ba.
31. Mehta Y, Arora D. Newer methods of cardiac output monitoring. World J Cardiol. 2014;6(9):1022–9.
32. Magnotti LJ, Upperman JS, Xu DZ, Lu Q, Deitch EA. Gut-derived mesenteric lymph but not portal blood increases endothelial cell permeability and promotes lung injury after hemorrhagic shock. Ann Surg. 1998;228(4):518–27.
33. Grossie VB Jr, Weisbrodt NW, Moore FA, Moody F. Ischemia/ reperfusion-induced disruption of rat small intestine transit is reversed by total enteral nutrition. Nutrition. 2001;17(11–12):939–43.
34. De-Souza DA, Greene LJ. Intestinal permeability and systemic infections in critically ill patients: effect of glutamine. Crit Care Med. 2005;33(5):1125–35.
35. Zaloga GP, Roberts PR, Marik P. Feeding the hemodynamically unstable patient: a critical evaluation of the evidence. Nutr Clin Pract. 2003;18(4):285–93.
36. Larson SD, Li J, Chung DH, Evers BM. Molecular mechanisms contributing to glutamine-mediated intestinal cell survival. Am J Physiol Gastrointest Liver Physiol. 2007;293(6):G1262–71.
37. Kreymann KG, Berger MM, Deutz NEP, et al. DGEM (German Society for Nutritional Medicine), Ebner C, Hartl W, Heymann C, Spies C, ESPEN (European Society for Parenteral and Enteral Nutrition). ESPEN Guidelines on Enteral Nutrition: Intensive care. Clin Nutr. 2006;25(2):210–23.
38. McClave SA, Martindale RG, Vanek VW, et al. A.S.P.E.N. Board of Directors, American College of Critical Care Medicine, Society of Critical Care Medicine. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). J Parenter Enter Nutr. 2009;33(3):277–316.

Neurological Dysfunction in Multiple Organ Failure in Trauma

10

Cynthia Bierl

10.1 Introduction: Acute Cognitive Dysfunction Secondary to MOF in Trauma

Neurological dysfunction in MOF from trauma can be described from the bedside assessment, the proposed pathological mechanisms, or retrospectively by the long-term neurological outcomes associated with the syndrome. The heralding feature of neurological dysfunction in MOF is the presence of delirium [1]. Delirium is a syndrome of acutely altered mental state which fluctuates over time [2]. It presents in three phenotypes of hyperactive, mixed, or hypoactive delirium [3]. Altered arousal, disorganised thinking, inattention, anhedonia, perceptual disturbances, psychosis and altered sleep-wake cycle are distributed across phenotypes. Delirium is associated with adverse outcomes including functional decline, permanent deficits in cognition and increased mortality [4].

10.2 Proposed Pathological Mechanisms: Neuroinflammation

Major trauma results in severe local and systemic inflammatory cascade initially from the direct injury to tissue from impact and physical injury, and secondarily from the resuscitative surgical and hemodynamic measures to repair damaged and re-perfuse ischemic tissues.

The initial response is termed the systemic inflammatory response (SIRS). In SIRS, powerful pro-inflammatory immunomediators, like NF-Kb, IL-1 and TNF-alpha, cause endothelial dysfunction which in turn cause increased capillary permeability, vasodilation and activation of the coagulation cascade [5–7]. Simultaneously

C. Bierl (✉)
Department of Intensive Care, John Hunter Hospital, Newcastle, NSW, Australia
e-mail: cynthia.bierl@health.nsw.gov.au

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_10

with the pro-inflammatory mediators the compensatory anti-inflammatory regulators (CARS) are also triggered, which act to immunosuppress and immune-regulate but predispose to infection. Sustained, out of control hyper-inflammation and/or infection is hypothesized to fuel a persistent pro-inflammatory state [7]. The 'immune dissonance' among regulatory mechanisms leads to a cytokine and endocrine storm thought to cause many of the observations at the critical care bedside in polytrauma: vasodilatory shock, fever, tachycardia, thrombosis, infection and organ dysfunction [8].

Neuroinflammation in MOF has predominantly been explored in the post-operative and septic patient, but likely shares a common pathway in trauma [5, 8]. The neuroinflammatory hypothesis poses that an acute stressor, such as surgery, infection or trauma, triggers SIRS that extends into the brain and ultimately can lead to long-term cognitive dysfunction. Similar to systemic hypotheses, the proposed mechanism is the disruption of the blood-brain barrier, via endothelial dysfunction triggered by overzealous or sustained low-grade systemic inflammation [8]. The invasion of brain interstitium by humoral and cellular elements cause neuroinflammation and microglial activation. This elevation of pro-inflammatory mediators in the brain has been shown to cause deficits in attention, memory and executive function [9].

Of importance, age is an independent and strong predisposing risk factor for poor cognitive outcomes in MOF, partially due to impaired ability to regenerate and heightened inflammatory state [10, 11]. The immune system is predisposed to chronic inflammation as the body ages. This baseline pro-inflammatory state, termed 'inflammaging', likely contributes to the dysregulation of SIRS and CARS in MOF [11, 12]. Interestingly, many of the mediators of neuroinflammation in MOF pathologically converge with better studied chronic neuroinflammatory conditions, e.g. Alzheimer's type dementia. The shared pathways explain why patients with pre-existing cognitive decline have worse cognitive outcomes and also provide some explanation for the cross-over in symptoms in PICS with dementia-type cognitive decline [13]. High-income countries have aging populations with higher presentations of multi-trauma in the elderly and frail, many of whom have clear expectations for acceptable cognitive outcomes in their health-care. This underscores the need for a clear prognostic understanding of the impact of MOF on long-term cognitive morbidity to help guide expectations for clinical teams and patients.

10.3 Early Neurological Failure: Delirium

The best available tools for monitoring and diagnosing acute confusion and delirium are the Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC) [3]. Both tools measure elements of level of consciousness, inattention, disorientation, psychosis, psychomotor agitation or slowing, mood and sleep/wake cycles [3].

Delirium is classified into three phenotypes of hyperactive, mixed motor type and hypoactive delirium. Hyperactive phenotypes are characterized by higher

incidence of agitation, hallucintations, and acute psychosis. Hypoactive delirium has less psychosis features and more anhedonia, inattention, and drowsiness. With a more subtle bedside presentation, hypoactive delirium is underdiagnosed, but has greater mortality, longer length of stay, worse quality of life and greater frequency of re-hospitalisation. Evidence further suggests in studies that actively screen for delirium, 50% of delirium diagnoses are of the hypoactive phenotype [14].

The burden of delirium in trauma patients is high with one study reporting 24% of patients in intensive care and step-down high dependency units positive for delirium. Although not independent, mechanical ventilation is strongest surrogate predictor for delirium where evidence suggests up to 80% of patients are affected. Other predictors of delirium include pre-existing cognitive disorders, hypertension, older age, medication (especially benzodiazepines and opioids) and metabolic acidosis. Up to 50% of patients with acute delirium will have long-term cognitive deficits at 12 months [15]. With a strong correlation to cognitive impairment and in-hospital mortality, systems are moving towards incorporating surveillance methods to measure it.

10.4 Late Neurological Failure: Post-intensive Care Syndrome

While early diagnosis and differentiation of neuroinflammation from MOF in trauma is sometimes obscured by confounding and complex clinical presentations, the longer-term sequelae of declines in cognitive, physical and psychiatric function continue post-acute hospitalisation. The Society of Critical Care Medicine created the term Post-Intensive Care Syndrome (PICS) to describe these impairments, specifically excluding direct tissue damage aetiology like traumatic brain injury or stroke [16]. The pathology of PICS is still considered multifactorial, but within PICS it is estimated that 80% of adult intensive care survivors have longer-term cognitive impairment. This is characterised by impairments in memory, processing speed and attention. Neuroinflammation of MOF contributes to the cascade of factors leading to this outcome [17, 18].

10.5 Impact of Neurological Failure on Outcomes in MOF

To measure the impact of MOF in Trauma, composite scoring systems of organ dysfunction correlate and predict mortality and morbidity. Unfortunately, existing composite scores are poorly sensitive for neurological dysfunction [19]. Organ failure is usually defined and diagnosed by either the support that is required to help that failing system or the physiologic derangement that resulted in that support [19]. However, both of these diagnostic measures are difficult to numerically quantify in neurological dysfunction where the observable derangements, like fluctuating confusion and attention, and therapeutics aren't on a predictable spectrum or titratable to a response. Additionally, attributing the diagnosis of acute neurological

dysfunction to MOF alone is also difficult in polytrauma patients with the confounding presence of traumatic brain injury, secondary brain injury due to hypoperfusion of metabolic derangements or the presence of sedation, analgesia and anaesthesia.

There are many scoring systems utilised to measure and diagnose MOF in trauma. These include the SOFA, Denver, APACHE, SAPS and MODS scores [20, 21]. The composite values utilise measures ubiquitous in modern bedside critical care and make their universal calculation useful for research and defining severity and predicting prognosis. Some of them diagnose MOF as an all or nothing phenomenon and some describe it rather on the continuous spectrum of multiple organ dysfunction syndrome (MODS). They have validated predictability in outcomes and prognosis and can be used for quality measures [20]. However, only four of the scoring systems incorporate measures of neurological dysfunction and for this, they incorporate the Glasgow Coma Score (GCS).

The GCS was developed in 1974 by neurosurgeons with measures for eye-opening, motor and verbal responses. The aggregate score is summary score for overall severity and is a useful field measure for severity of acute direct brain injury [22]. However, its sensitivity and specificity in discerning the neurological dysfunction in MOF is questionable. The heralding feature of brain failure in MOF is an acute confusional state and delirium. Diagnosis of delirium requires identification of confusion, impaired attention, impaired cognition, and/or psychosis with temporal fluctuation in the same. The GCS does not measure these symptoms and therefore current MOF scoring systems likely poorly quantify neurological failure. Therefore the impact, severity and prevalence of neurological dysfunction in MOF is also poorly described.

However, delirium and acute confusional states are strong and independent predictors of higher healthcare costs, poorer longterm function and increased mortality. For this reason, bedside measures of delirium are being incorporated into hospital early warning systems and are increasingly being reported as hospital-acquired complications [23]. Given the impact of delirium on patient outcomes, a MOF score that incorporates it may significantly improve the accuracy of these scores in predicting outcomes for the severe trauma population.

10.6 Management and Prevention

In complex trauma, the path to central neurological dysfunction has multiple origins. First, the direct insult to the brain due to regional energy deprivation or tissue injury from the traumatic event. The direct insult could cause regional hypoxia, hypoglycaemia, infarction and/or acidosis leading to metabolic strain. The neuroinflammatory hypothesis poses that subsequent to the original trauma a distinct indirect insult occurs in the brain due to the aberrant stress responses of the body in inflammation [4, 24]. In addition, trauma patients are given analgesia, sedation and often anaesthesia which all have independent risks for acute neurocognitive dysfunction. At the bedside, these mechanisms converge into similar symptoms,

probably share driving mechanisms, and therefore differentiating between the drivers of cognitive dysfunction becomes difficult. However, bedside diagnosis of the driving cause of delirium is academic, as there is a lack of targeted therapeutics for neurologic support in neuroinflammation. The support of the directly injured brain is outside the scope of this chapter although many of the principles of neuroprotection are the same.

With a lack of specific therapeutics, management and prevention of neurological dysfunction remains multifaceted and thought to be best implemented by a multidisciplinary team that include critical care nurses, physiotherapists, pharmacists and respiratory therapists. The ABCDEF bundle represents an example of an evidence-based protocolised approach to supportive care of the critically unwell patient with a focus on delirium management and prevention [3, 16]. The principles will be discussed here.

A. Assess, Prevent and Manage Pain. Pain is an underdiagnosed and undertreated but frequent symptom in the critically injured trauma patient. Pain increases agitation, increases the stress response, and poor management of pain likely contributes to delirium and predisposes to long-term sequelae of chronic pain. Despite this, evidence suggests in critically unwell patients it is often poorly measured [3].
B. Both spontaneous awakening and spontaneous breathing trials.
For the ventilated patient, daily interruption of sedation and when appropriate, breathing trials, have been shown to decrease ventilation time and decrease incidence of delirium. Sedation should be monitored, titrated and not be used to treat pain. Interestingly, a trial of no sedation in ventilated intensive care patients has been evaluated, which similarly showed the benefits of decreased ventilation time but at a cost of increased hyperactive delirium. Deep sedation has consistently been shown to be associated with longer ventilation times and increased mortality [3].
C. Choice of analgesia and sedation. The ideal agents for sedation and analgesia should be patient specific. There is a clear association between benzodiazepines and increased delirium. Recreational and prescibed psychotropic withdrawal may contribute to delirium. Therefore, early surveillance through collateral pharmacological and drug and alcohol history are critical in preventing subsequent delirium. Alpha-2-agonist sedatives have mixed evidence of reduced incidence of delirium and at least, less harmful than benzodiazepines. However, this is at the cost of potential hemodynamic effects of bradycardia, hypotension, and in severe cases, sinus pause. However, it is widely used to control agitation in delirium and neuro-recovery [3].
D. Delirium: assess, prevent, manage: The majority of intensive care patients develop delirium with average onset on the second or third day of admission. Validated tools like the CAM-ICU or the ICDSC should be used for surveillance and monitoring of delirium. Once identified, patients benefit from a protocolised approach to management and treatment of reversible causes, like alcohol or opiate withdrawal or electrolyte abnormalities. Alpha-agonists, at best, probably

don't aggravate delirium. Anti-psychotics assist to prevent self-harm and sedate in agitated delirium. There are no proven pharmacological therapeutics available to reverse delirium. Environmental factors and staffing have some evidence of benefit for the delirium. These interventions include promoting good sleep hygiene, access to natural light, clustering of nursing cares to minimise sleep disruption cares, and presence of family and familiar carers [3].

E. Early engagement and mobility. Early mobility has been proven to decrease days of delirium. To achieve early mobility in the sedated severely injured patient requires multidisciplinary engagement of teams. Trauma surgical teams need to promptly complete the primary and secondary survey. Radiological services need to promptly review images and rule-out spinal injury so patients can be woken safely. Extended days of ventilation and sedation due to spinal instability and the need for spinal precautions dramatically increases the risk for ventilator-acquired pneumonia, secondary infection, and thrombosis. Immobility also leads to stress, acute weakness and long-term functional limitation. Therefore, timely clearance or stabilisation of the axial skeleton and long bones is essential for optimal positioning and mobilisation. Physiotherapy is feasible, safe and complicated patients on advanced supportive therapies should not be viewed as an impediment to mobilisation. However, safe staffing and trained critical care physiotherapy teams are critical to implementing it.

F. Family engagement and empowerment. In critical care, family members are surrogate decision-makers, care advocates and helpful at the bedside to re-orient recovering critically ill patients.

Strategies targeting the bundled approach to care have been shown in randomised-control trials to significantly reduce duration of delirium, decrease ventilation time and improve functional outcomes at hospital discharge [25–27].

10.7 Future Directions

Evidence shows a strong repeated association between the systemic inflammatory response, neuroinflammation, acute delirium, and patient death and poor neurological outcomes. The potential for length of stay, need for community support and long-term functional disability also carry significant financial and community burdens. Despite this there are no targeted therapies or recent trials of targeted therapies for preventing neurological dysfunction in MOF. However, immunotherapies designed for autoimmune conditions may prove useful in combating the detrimental effects of SIRS [28]. Interleukin-6 (IL-6) is a cytokine involved in the inflammatory regulatory cycle. Anti-IL 6 receptor antibodies, or tocilizumab, have been given therapeutically for autoimmune conditions with success and may extend utility in preventing the organ dysfunction in SIRS [29]. Neuroinflammation is widely underdiagnosed but with significant and meaningful impacts for patients who survive MOF. Advancing therapeutics in immunomodulation are promising but not yet proven.

References

1. Bullock CR, et al. Delirium in critically ill military patients following trauma: a cohort analysis. J Intensive Care Soc. 2016;17(1):12–8.
2. Johnson K, et al. Early recognition of delirium in trauma patients. Intensive Crit Care Nurs. 2016;34:20–4.
3. Marra A, et al. The ABCDEF bundle in critical care. Crit Care Clin. 2017;33(2):225–43.
4. Maclullich AM, et al. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. J Psychosom Res. 2008;65(3):229–38.
5. Katsumi Y, et al. The Role of Inflammation after Surgery for Elders (RISE) study: examination of [(11)C]PBR28 binding and exploration of its link to post-operative delirium. Neuroimage Clin. 2020;27:102346.
6. Lenz A, Franklin GA, Cheadle WG. Systemic inflammation after trauma. Injury. 2007;38(12):1336–45.
7. Hshieh TT, et al. The Role of Inflammation after Surgery for Elders (RISE) study: study design, procedures, and cohort profile. Alzheimers Dement (Amst). 2019;11:752–62.
8. Alam A, et al. Surgery, neuroinflammation and cognitive impairment. EBioMedicine. 2018;37:547–56.
9. Hirsch J, et al. Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery. J Neuroinflammation. 2016;13(1):211.
10. Bryczkowski SB, et al. Risk factors for delirium in older trauma patients admitted to the surgical intensive care unit. J Trauma Acute Care Surg. 2014;77(6):944–51.
11. Cyr B, de Rivero Vaccari JP. Age-dependent microglial response to systemic infection. Cell. 2021;10(5):1037.
12. Daiello LA, et al. Postoperative delirium and postoperative cognitive dysfunction: overlap and divergence. Anesthesiology. 2019;131(3):477–91.
13. Vasunilashorn SM, et al. New delirium severity indicators: generation and internal validation in the better assessment of illness (BASIL) study. Dement Geriatr Cogn Disord. 2020;49(1):77–90.
14. Hosker C, Ward D. Hypoactive delirium. BMJ. 2017;357:j2047.
15. Goldberg TE, et al. Association of delirium with long-term cognitive decline: a meta-analysis. JAMA Neurol. 2020;77(11):1373–81.
16. Ahmad MH, Teo SP. Post-intensive care syndrome. Ann Geriatr Med Res. 2021;25(2):72–8.
17. Smith S, Rahman O. Post intensive care syndrome. Treasure Island, FL: StatPearls; 2021.
18. Mira JC, et al. Sepsis pathophysiology, chronic critical illness, and persistent inflammation-immunosuppression and catabolism syndrome. Crit Care Med. 2017;45(2):253–62.
19. Shepherd JM, Cole E, Brohi K. Contemporary patterns of multiple organ dysfunction in trauma. Shock. 2017;47(4):429–35.
20. Frohlich M, et al. Which score should be used for posttraumatic multiple organ failure? - Comparison of the MODS, Denver- and SOFA- Scores. Scand J Trauma Resusc Emerg Med. 2016;24(1):130.
21. Hutchings L, et al. Defining multiple organ failure after major trauma: a comparison of the Denver, Sequential Organ Failure Assessment, and Marshall scoring systems. J Trauma Acute Care Surg. 2017;82(3):534–41.
22. Jain S, Iverson LM. Glasgow coma scale. Treasure Island, FL: StatPearls; 2021.
23. Dharmarajan K, et al. Pathway from delirium to death: potential in-hospital mediators of excess mortality. J Am Geriatr Soc. 2017;65(5):1026–33.
24. Vasunilashorn SM, et al. Plasma and cerebrospinal fluid inflammation and the blood-brain barrier in older surgical patients: the Role of Inflammation after Surgery for Elders (RISE) study. J Neuroinflammation. 2021;18(1):103.
25. Schweickert WD, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373(9678):1874–82.

26. Trogrlic Z, et al. A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes. Crit Care. 2015;19:157.
27. Cole E, et al. Multiple organ dysfunction after trauma. Br J Surg. 2020;107(4):402–12.
28. Darville T, Giroir B, Jacobs R. The systemic inflammatory response syndrome (SIRS): immunology and potential immunotherapy. Infection. 1993;21(5):279–90.
29. Kang S, Tanaka T, Kishimoto T. Therapeutic uses of anti-interleukin-6 receptor antibody. Int Immunol. 2015;27(1):21–9.

Post-injury Multiple Organ Failure: Respiratory Failure

11

Joseph Galante and Eric Shurtleff

11.1 Introduction

Post-injury respiratory failure is defined as inadequate gas exchange secondary to dysfunction of the chest wall, alveoli, pulmonary circulation, or central nervous system [1]. Acute Respiratory Distress Syndrome (ARDS) develops in 12–25% of traumatically injured patients, and the lungs are the most common organ system affected in post-injury multiple organ failure (MOF). Mortality in injured patients with ARDS and MOF has been reported to range as high as 34–64% [2].

The etiologies of hypoxia and hypercapnia of post-injury respiratory failure include both direct chest trauma and extra-thoracic or indirect injury. Direct blunt chest injuries precipitating respiratory failure include rib fractures, flail chest, pneumothorax, and pulmonary contusions, all of which trigger a systemic inflammatory response. Penetrating chest trauma is also a cause of respiratory failure, as it affects the lung tissue directly as well as initiating a systemic inflammatory response. High mortality rates are reported in patients requiring operative management, ranging from 62% for pneumonectomy, 35% for lobectomy to 22% for wedge resection [3].

Traumatic brain injury (TBI) is an extra-thoracic cause of post-injury respiratory failure resulting from impaired central nervous system (CNS)-mediated respiratory drive and other pathophysiologic response to brain injury. Up to 33% of TBI patients develop respiratory failure to some extent [4]. Venous thrombosis, pulmonary embolus, and primary pulmonary thrombosis which are commonly identified early in the post-injury phase, are another indirect cause of respiratory failure [5, 6].

J. Galante (✉)
Department of Surgery, University of California, Davis, Sacramento, CA, USA
e-mail: jmgalante@ucdavis.edu

E. Shurtleff
Maine Medical Partners Acute Care Surgery, Portland, ME, USA

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_11

Femur fractures represent another mechanism of an extra-thoracic, indirect cause of post-injury respiratory failure [7].

Finally, severely injured polytrauma patients commonly require shock resuscitation, infused crystalloid and transfusion volumes can be massive. Risk of ARDS is directly correlated with crystalloid infusion, transfusion of packed red blood cells and fresh frozen plasma, and can be difficult to prevent given the life-saving necessity of massive transfusion in the early post-injury period [8–10].

Understanding the causes of post-injury respiratory failure, while important given the differing approaches to treating them, is not as important as grasping the impact of invasive and noninvasive support. While invasive and noninvasive respiratory support are necessary, if not implemented appropriately, either modality can exacerbate post-injury respiratory failure by iatrogenic secondary injuries.

11.2 Pathophysiology

Acute respiratory failure is generally the result of two conditions: hypoxia and hypercapnia, which can precipitate failure independently or simultaneously. Hypoxia is defined as $PaO_2 < 50$ mmHg, and hypercapnia is defined as $PCO_2 > 45$ mmHg, with decreased minute ventilation (see Table 11.1).

11.2.1 Hypoxia

One mechanism of hypoxia occurs when *alveoli are perfused but not ventilated*, and therefore not oxygenated. This is defined as intra-pulmonary shunt, which occurs in alveolar collapse, pulmonary edema, pulmonary contusions, ARDS, and pulmonary collapse/pneumothorax. A second mechanism of hypoxia occurs when alveoli are *ventilated but not perfused*. This ventilation/perfusion (V/Q) mismatch dysfunction occurs at the alveolar capillary level and is provoked by pulmonary embolism, primary pulmonary thrombosis, and pulmonary hypertension, wherein alveolar circulatory compromise prevents the uptake of oxygen provided by the ventilated lung.

Table 11.1 Hypoxia and Hypercapnia: definitions, etiologies, pathophysiology

Hypoxia	Hypercapnia
$PaO_2 < 50$ mmHg	$PCO_2 > 45$ mmHg
Shunt: Alveolar collapse, pulmonary edema, pulmonary contusions, pneumothorax/collapse, ARDS	Hypoventilation: Pain, CNS depression due to traumatic brain injury, narcotic-induced CNS impairment, poor compliance: Chest wall deformity, obesity
V/Q mismatch: Primary pulmonary thrombosis, embolus, pulmonary hypertension	Decreased functional residual capacity (FRC) decreased minute ventilation (MV)

11.2.2 Hypercapnia

The primary etiologies of hypercapnic respiratory failure include: pain, central nervous system (CNS) depression due to traumatic brain injury, narcotic-induced CNS impairment, and poor compliance, i.e., chest wall deformity, obesity, where compliance is defined as change in volume divided by change in pressure. Hypercapnia is generally precipitated by two mechanisms. One mechanism is decreased functional residual capacity (FRC) results from increased "dead space," which is the volume of air that is ventilated but not involved in gas exchange. Dead space has two components, anatomic and physiologic. Anatomic dead space is approximately 30% of the normal tidal volume (V_T), and physiologic or total dead space is the sum of anatomic dead space and alveolar dead space, which is defined as the volume of air in the respiratory zone that does not exchange gas across the alveolar epithelium. The anatomic dead space is a fixed value, whereas physiologic dead space is increased in pathophysiologic states such as ARDS [11–13]. The second mechanism is decreased minute ventilation (MV), which is defined as: MV = (V_T) × (Respiratory Rate (f)) (see Table 11.2).

11.2.3 Pathophysiology due to Mechanism of Injury

The pathophysiology of acute respiratory failure due to ARDS stems from both direct and indirect lung injury. Direct injuries precipitating ARDS include chest wall trauma, pulmonary contusions, pulmonary lacerations, and pneumothorax. ARDS develops in this setting due to provocation of the innate immune response via enhanced reactivity of toll-like receptor 4 (TLR-4). This in turn induces exaggerated pro-inflammatory mediators known to evolve in the early phase of trauma: IL-1beta, IL-6, IL-8, which induce a systemic pro-inflammatory response. This is thought to sustain in the case of rib fractures and paradoxical chest wall motion in flail chest, which exacerbate the underlying contused lung parenchyma with ventilation [16].

Severe extra-thoracic tissue injury due to trauma or surgery is a known indirect cause of acute respiratory failure. In TBI, injury to the central nervous system

Table 11.2 Definitions of lung capacities and volumes, with normal values [14, 15]

Lung capacity/volume	Definition	Normal value (adult male)
Total lung capacity (TLC)	IRV + ERV + RV + V_T	4000–6000 mL
Vital capacity (VC)	IRV + V_T + ERV	4800 mL (varies with age/body size)
Functional residual capacity (FRC)	ERV + RV	1800–2200 mL
Inspiratory capacity (IC)	V_T + IRV	2400–3800 mL
Tidal volume (V_T)		500 mL (10% of VC, 6–8 mL/kg)
Inspiratory reserve volume (IRV)		1900–3300 mL
Expiratory reserve volume (ERV)		700–1200 mL
Residual volume (RV)		1200 mL (20–25 mL/kg)

blunts respiratory drive, and increased endothelial permeability evolves at the blood-brain and the blood-lung barriers [17, 18]. Further, increased intracranial pressure in TBI has been demonstrated to precipitate pulmonary edema [19, 20].

Severe musculoskeletal injuries and subsequent surgeries are another indirect cause of pulmonary complications and ARDS, independent of chest trauma [7]. One proposed mechanism relates to interleukin-6, which is a known systemic pro-inflammatory mediator that increases risk of ARDS. IL-6 is increased in the plasma both after femur fracture and after femoral intramedullary nail placement [21].

11.3 Diagnosis

The diagnosis of respiratory failure in the current era is hardly more complex than in times prior to lab testing or sophisticated imaging modalities. Rapid and accurate diagnosis of acute respiratory failure continues to rely predominantly on clinical suspicion and evaluation of the patient at the bedside.

On physical exam, the patient with developing respiratory failure will typically have tachypnea, accessory muscle use, abdominal breathing, and diminished breath sounds on auscultation. Of these physical signs, tachypnea is probably the most reliable indicator of impending respiratory failure. On bedside monitoring, the percentage of oxygenated hemoglobin (SpO_2) will be decreased and/or the end-tidal carbon dioxide ($ETCO_2$) will be elevated. In some cases, there will be no sign of impending respiratory failure, and the patient will decompensate precipitously. In all cases, rapid diagnosis and treatment can be life-saving.

Measurement of arterial blood gas (ABG) is the gold standard for confirmation of the clinical diagnosis of acute respiratory failure. Caution must be exercised in interpreting the relationship of SpO_2 and the oxyhemoglobin dissociation curve, i.e., SpO_2 greater than 90% does not necessarily equate with a normal PaO_2. Peripheral venous blood gas is not as reliable and while it can be a surrogate, there are wide variations in PaO_2 and PCO_2, rendering it inferior to the ABG for establishing the diagnosis of respiratory failure definitively [22].

Chest radiographs and computed tomography (CT) of the chest are useful adjuncts to determine the underlying etiology precipitating respiratory failure, but are not necessary to diagnose the clinical condition. Both imaging modalities are best utilized *after* respiratory failure has been diagnosed and treatment has been implemented to stabilize the patient.

11.4 Treatment

The main principles of respiratory failure treatment are: (1) support the patient while identifying and treating the underlying cause, and (2) prevent further pulmonary injury while supporting recovery. The ARDSnet mechanical ventilator protocol provides an evidence-based means to implement these principles in patients with PaO_2/FiO_2 ratios $\leq$300, bilateral infiltrates consistent with pulmonary edema, and no evidence of left atrial hypertension (See Fig. 11.1) [23]. The lung-protective

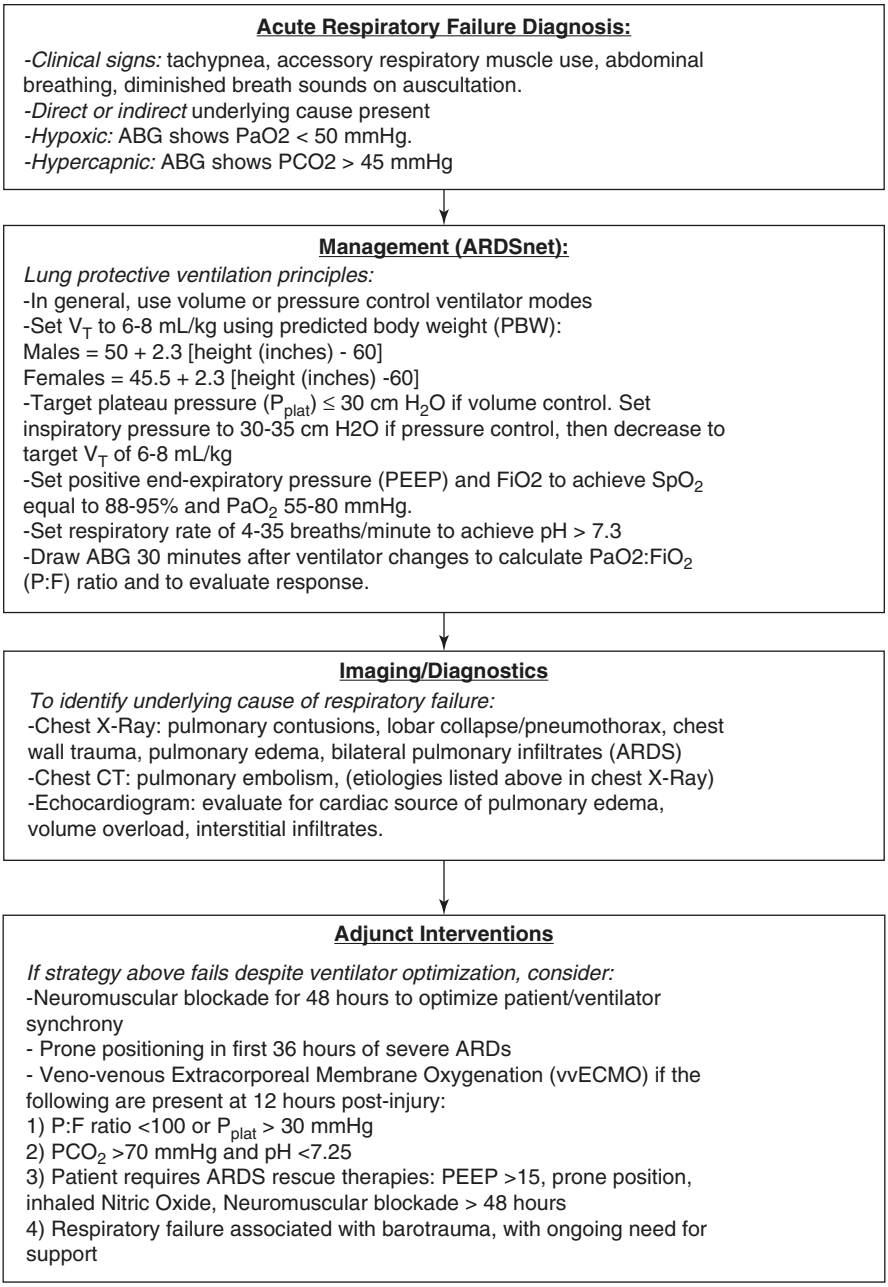


Fig. 11.1 Management of acute respiratory failure

ventilator strategy outlined by the ARDSnet group has further been demonstrated to improve outcomes in patients who do *not* have ARDS but require mechanical ventilation for another cause of respiratory failure, and therefore should be implemented where possible [24–26].

Other important principles of lung-protective ventilation include "driving pressure," permissive hypercapnia, and absorptive atelectasis, which represent normal physiologic and anatomic limitations of the lung. These concepts are essential to ongoing management of respiratory failure once ARDSnet protocol has been initiated.

Driving pressure is defined as $\Delta P = V_T/C_{RS}$ (where ΔP = change in pressure, V_T = tidal volume, and C_{RS} = compliance of the respiratory system, which is directly related to the volume of aerated lung). ΔP values of 7 cm H_2O are associated with increased mortality. Therefore, limiting V_T in the face of the decreased C_{RS} found in ARDS, chest trauma, pulmonary contusions, etc. is critical for survival. Compliance of the respiratory system is anatomically limited by the intra-thoracic diameter, and thus the upper limit of PEEP that can be tolerated is generally: (0.8) × (intra-thoracic diameter). Applying this clinically, "Driving Pressure" = P_{plat} – PEEP; and therefore P_{plat} should be maintained at 30 mmHg or less, which can be achieved by reducing V_T to 4–6 mL/kg, and PEEP should be titrated to maintain PaO_2 55–80 mmHg [27].

In order to achieve plateau pressures less than 30 mmHg and tidal volumes of 6 mL/kg, hypercapnia can result. The term, "permissive hypercapnia," describes the acceptance of elevated PCO_2 in ARDS in order to protect the lung from barotrauma. Permissive hypercapnia is well-described, generally well-tolerated, and is a useful means to reduce mortality and improve outcomes with lung-protective ventilation [28, 29].

At FiO_2 levels of 100%, absorptive atelectasis occurs due to washout of alveolar nitrogen. This process is not readily reversible by decreasing FiO_2 once it has occurred, and other means of alveolar recruitment become necessary [30]. In general, maintaining FiO_2 less than 60% will prevent absorptive atelectasis and other consequences of hyper-oxygenation.

When the ARDSnet lung-protective ventilator strategy fails, adjunctive rescue therapies can be attempted. These include prone positioning, veno-venous extracorporeal membrane oxygenation, high frequency oscillatory ventilation, and inhaled nitric oxide (iNO).

Prone positioning early in the course of post-injury ARDS can be used to enhance ventilatory support. Prone positioning improves alveolar aeration by displacing the weight of the heart, the lungs, and the chest wall anteriorly, allowing the posterior lungs to expand freely. Prone positioning in severe ARDS has been shown to improve oxygenation and reduce ventilator-associated lung injury [31, 32]. Prone positioning, within the first 36 h after the development of severe ARDS, was further shown by the PROSEVA randomized controlled trial to improve 28- and 90-day mortality, versus supine positioning [33].

Veno-venous extra-corporeal membrane oxygenation (VV-ECMO) is a rescue therapy used with increasing frequency in failure of lung-protective ventilation, as

has been shown to improve survival in adult trauma patients without significant increase in ICU or hospital length of stay, and further demonstrated no significant increase in hemorrhagic complications versus controls [34]. In general, VV-ECMO needs to be initiated early, before pulmonary-induced cardiac failure, and should be considered in severe respiratory failure at 12 h. While no universally accepted indications for VV-ECMO in respiratory failure currently exist, generally accepted indications, relative contraindications and contraindications are as follows:

11.4.1 Indications

- Severe hypoxemia (e.g., ratio of PaO_2 to Fio_2 < 80, despite the application of high levels of PEEP [typically 15–20 cm of water]) for at least 6 h in patients with potentially reversible respiratory failure.
- Uncompensated hypercapnia with acidemia (pH < 7.15) despite the best accepted standard of care for management with a ventilator
- Excessively high end-inspiratory plateau pressure (>35–45 cm of water, according to the patient's body size) despite the best accepted standard of care for management with a ventilator

11.4.2 Relative Contraindications

- High-pressure ventilation (end-inspiratory plateau pressure >30 cm of water) for >7 days
- High Fio_2 requirements (>0.8) for >7 days
- Limited vascular access
- Any condition or organ dysfunction that would limit the likelihood of overall benefit from ECMO, such as severe, irreversible brain injury or untreatable metastatic cancer
- Any condition that precludes the use of anticoagulation therapy [35]

VV-ECMO should therefore be considered in patients who develop the following at 12 h post-injury: (1) P:F ratio < 100 or P_{plat} > 30 mmHg, (2) PCO_2 > 70 mmHg and pH < 7.25, (3) Patient requires ARDS rescue therapies: PEEP >15, prone position, inhaled nitric oxide, neuromuscular blockade >48 h, and (4) Respiratory failure associated with barotrauma, with ongoing need for mechanical ventilator support. While historically TBI was a contraindication to ECMO due to intracranial bleeding risk, recent practice advances allow for initiation of VV-ECMO without heparinizing the circuit, and therefore use in patients with concomitant TBI and severe ARDS [36].

High frequency oscillatory ventilation (HFOV) is a modality used in children, and rarely in adults in the modern era. Two limitations of this ventilator mode are that the oscillator is traumatic to injured lung with low compliance and requires tolerance of high PCO_2. The main goal of HFOV is to deliver an extremely low V_T

with rapid oscillations to decrease mechanical injury and barotrauma; however, the resulting hypercapnia and acidosis require reducing the oscillatory frequency such that V_T approaches that applied by conventional mechanical ventilator modes, and the frequency with which the oscillator delivers these volumes induces volutrauma [37].

The role of inhaled nitric oxide (iNO) in ARDS and post-injury respiratory failure is as yet undefined. While iNO does improve oxygenation transiently, it has not been shown to reduce mortality. Further, iNO is associated with renal injury and failure [38].

11.5 Outcomes and Long-Term Effects

The over-arching disease severity of post-injury respiratory failure/ARDS is underscored by outcomes in the adult population, with in-hospital mortality reaching 40% and 5-year mortality at 60% [38, 39]. Long-term pulmonary sequelae are generally related to reduced diffusion capacity, but this has been found, in long-term observational studies, to have less impact on overall function as the neuromuscular and neurocognitive consequences of the disease [38]. This is not to say that the pulmonary fibrosis that persists after the disease has run its course is insignificant. Current thinking proposes that, contrary to the previous hypothesis that ARDS followed a generalized progression of endothelial and epithelial damage, exudation and inflammation, fibroproliferation; it may be that fibroproliferation, exudation and inflammation actually occur simultaneously [40]. Ultimately, why the lung recovers or progresses to fibrosis is unknown, but trials are ongoing to determine if IV corticosteroid therapy or other anti-fibrotic regimens have a role in the mitigation of fibrosis in late ARDS [41].

11.6 Conclusion

Respiratory failure and ARDS are devastating consequences of severe traumatic injury. Unlike other injury-associated disease states, diagnosis continues to rely upon clinical assessment at the bedside and ABG analysis alone, despite the technologic sophistication of medicine in the modern era. Treatment can be generally divided into two main goals: (1) support the patient's respiratory function while identifying and treating the underlying cause of failure; and (2) avoid further iatrogenic injury to the lung with support. Both goals can be accomplished by utilizing the relatively simple ventilator strategies outlined in the ARDSnet lung-protective ventilator strategy protocol. Adjunctive rescue therapies when ARDSnet fails, such as prone positioning and ECMO, are possible but limited by resources in many practice environments.

References

1. Noorbakhsh MR, Kriley IR. Management of severe respiratory failure in complex trauma patients. J Emerg Crit Care Med. 2018;2:26.
2. Del Sorbo L, Slutsky AS. Acute respiratory distress syndrome and multiple organ failure. Curr Opin Crit Care. 2011;1:1–6.
3. Martin MJ, McDonald JM, Mullenix PS, et al. Operative management and outcomes of traumatic lung resection. J Am Coll Surg. 2006;203:336–44.
4. Pelosi P, Severgnini P, Chiaranda M. An integrated approach to prevent and treat respiratory failure in brain-injured patients. Curr Opin Crit Care. 2005;11:37–42.
5. Menaker J, Stein DM, Scalea TM. Incidence of early pulmonary embolism after injury. J Trauma. 2007;63:620–4.
6. Shutzman LM, Rigor RR, Khosravi N, Galante JM, Brown IE. P-selectin is critical for de novo pulmonary arterial thrombosis following blunt thoracic trauma. J Trauma Acute Care Surg. 2019;86:4.
7. Lafaivre KA, Starr AJ, Stahel PF, Elliott AC, Smith WR. Prediction of pulmonary morbidity and mortality in patients with femur fracture. J Trauma Inj Inf Crit Care. 2010;69(6):1527–36.
8. Chaiwat O, Lang JD, Vavilala MS, et al. Early packed red blood cell transfusion and acute respiratory distress syndrome after trauma. Anesthesiology. 2009;110:351–60.
9. Silverboard H, Aisiku I, Martin GS, et al. The role of acute blood transfusion in the development of acute respiratory distress syndrome in patients with severe trauma. J Trauma. 2005;59:717–23.
10. Watson GA, Sperry JL, Rosengart MR, et al. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. J Trauma. 2009;67:221–7. discussion 228–30
11. Coppola S, Froio S, Marino A, et al. Respiratory mechanics, lung recruitability, and gas exchange in pulmonary and extrapulmonary acute respiratory distress syndrome. Crit Care Med. 2019;47(6):792–9.
12. Huang B, De Vore D, Chirinos C, et al. Strategies for recruitment and retention of underrepresented populations with chronic obstructive pulmonary disease for a clinical trial. BMC Med Res Methodol. 2019;19(1):39.
13. Kiefmann M, Tank S, Tritt MO, et al. Dead space ventilation promotes alveolar hypocapnia reducing surfactant secretion by altering mitochondrial function. Thorax. 2019;74(3):219–28.
14. Raghavendran K, Park P, Bartlett R. Pulmonary insufficiency and respiratory failure. In: Ashley SW, editor. ACS surgery: principles and practice. Hamilton, ON: Decker; 2014. p. 2287–303.
15. Physiopedia contributors. Lung volumes. Physiopedia, [Internet]. https://www.physiopedia.com/index.php?title=Lung_volumes&oldid=208780. Accessed 18 July 2019.
16. Simon B, Ebert J, Bokhari F, Capella J, et al. Management of pulmonary contusion and flail chest: an Eastern Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg. 2012;73:S351–61.
17. Yildirim E, Solaroglu I, Okutan O, et al. Ultrastructural changes in tracheobronchial epithelia following experimental traumatic brain injury in rats: protective effect of erythropoietin. J Heart Lung Transplant. 2004;23:1423–9.
18. Rhodes JK, Andrews PJ, Holmes MC, et al. Expressionof interleukin-6 messenger RNA in a rat model of diffuse axonal injury. Neurosci Lett. 2002;335:1–4.
19. Ducker TB. Increased intracranial pressure and pulmonary edema. 1. Clinical study of 11 patients. J Neurosurg. 1968;28:112–7.
20. Malik AB. Mechanisms of neurogenic pulmonary edema. Circ Res. 1985;57:1–18.
21. Pesic G, Jeremic J, Nikolic T, et al. Interleukin 6 as possible early marker of stress response after femur fracture. Mol Cell Biochem. 2017;430:191–9.

22. Byrne AL, Bennett M, Chatterji R, Symons R, Pace NL, Thomas PS. Peripheral venous and arterial blood gas analysis in adults: are they comparable? A systematic review and analysis. Respirology. 2014;19(2):168–75.
23. NHBLI ARDS Network. Ventilator protocol card [Internet]. https://www.ardsnet.org/files/ventilator_protocol_2008-07.pdf. Cited 21 July 2019.
24. Serpo NA, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA. 2012;308(16):1651–9.
25. Futier E, Constantin J-M, Paugum-Burt C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. N Engl J Med. 2013;369(16):428–37.
26. Petrucci N, De Feo C. Lung protective ventilation strategy for the acute respiratory distress syndrome. Cochrane Database Syst Rev. 2013;2:CD003844.
27. Amato MBP, Meade MO, Slutsky AS, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med. 2015;372(8):747–55.
28. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med. 1990;16:372–7.
29. Hickling KG, Walsh J, Henderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med. 1994;22:1568–78.
30. Santos C, Ferrer M, Roca J, et al. Pulmonary gas exchange response to oxygen breathing in acute lung injury. Am J Respir Crit Care Med. 2000;161:26.
31. Mentzelopoulos SD, Roussos C, Zakynthinos SG. Prone position reduces lung stress and strain in severe acute respiratory distress syndrome. Eur Respir J. 2005;25:534–44.
32. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and metaanalysis. Intensive Care Med. 2010;36:585–99.
33. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368:2159–68.
34. Guirand DM, Okoye OT, Schmidt BS, et al. Venovenous extracorporeal life support improves survival in adult trauma patients with acute hypoxemic respiratory failure: a multicenter retrospective cohort study. J Trauma Acute Care Surg. 2014;76(5):1275–81.
35. Brodie D, Bachetta M. Extracorporeal membrane oxygenation for ARDS in adults. N Engl J Med. 2011;365:1905–14.
36. Muellenbach RM, Kredel M, Kunze E, et al. Prolonged heparin-free extracorporeal membrane oxygenation in multiple injured acute respiratory distress syndrome patients with traumatic brain injury. J Trauma Acute Care Surg. 2012;72(5):1444–7.
37. Sklar MC, Fan E, Goligher EC. High-frequency oscillatory ventilation in adults with ARDS. Chest. 2017;152(6):1306–17.
38. Rubenfeld GD, Herridge MS. Epidemiology and outcomes of acute lung injury. Chest. 2007;131:2.
39. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364:14.
40. Marshall R, Bellingan G, Laurent G. The acute respiratory distress syndrome: fibrosis in the fast lane. Thorax. 1998;53:815–7.
41. Meduri GU, Chinn AJ, Leeper KV, et al. Corticosteroid rescue treatment of progressive fibroproliferation in late ARDS. Patterns of response and predictors of outcome. Chest. 1994;105:1516–27.

Cardiac Failure

12

Kazuhide Matsushima and Demetrios Demetriades

12.1 Introduction

Of multiple organs affected in patients with multiple organ failure (MOF), the incidence of cardiac failure is around 20% in a large multicenter study from the USA, while more than half of study patients developed pulmonary failure [1]. In contrast, a more recent study from 29 UK trauma centers in which multiorgan dysfunction syndrome (MODS) was defined using the Sequential Organ failure Assessment (SOFA) scoring showed that both cardiac and pulmonary dysfunction were the greatest contributors to the diagnosis of MODS (91.0% and 97.1%, respectively) [2]. Although these discrepancies in the incidence of post-injury cardiac failure might be due to the two different scoring systems used in each study (the Denver MOF scoring system and SOFA scoring system), it is noteworthy that cardiovascular dysfunction was the most prominent during the initial days in the intensive care unit (ICU) and up to 24% of patients died in this phase. In addition, systemic inflammatory and immune responses induced by traumatic injury and subsequent complications (e.g. sepsis) can lead to persistent inflammation, immunosuppression, and catabolism syndrome (PICS) which aggravates the initial cardiac damage. Along with the results in another prospective study, it is suggested that cardiac failure would be the major component of MODS in the era of modern trauma care [3].

K. Matsushima · D. Demetriades (✉)
Department of Surgery, Division of Acute Care Surgery, University of Southern California, LAC+USC Medical Center, Los Angeles, CA, USA
e-mail: kazuhide.matsushima@med.usc.edu; demetria@usc.edu

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_12

12.2 Etiology

Following traumatic injury, it is well known that cardiac failure can be caused by various conditions including preexisting comorbidities and/or specific injury patterns (Table 12.1). As the population ages, an increasing number of elderly patients have been admitted for the management of various injuries [4]. Approximately 3% of all trauma patients admitted to the hospital have a history of heart failure [5]. A retrospective study using the National Trauma Data Bank (NTDB) showed that 28.7% of trauma patients with history of congestive heart failure developed major complications, and once they developed complications during the hospital stay, the mortality rate almost tripled (7.8% without complications vs. 21.8% with complications) [6]. Similarly, patients with history of myocardial infarction were 40% more likely to die after major complications. Direct injuries to the heart are more frequently seen, compared to blunt trauma, in patients presenting following penetrating thoracic trauma (gunshot wounds, stab wounds). Interestingly, an autopsy study from Los Angeles County showed that 32% of fatal blunt trauma victims (69.1% died at scene) were found to have cardiac injuries and most of them sustained transmural rupture [7].

A resuscitative thoracotomy (emergency department thoracotomy: EDT) is often indicated in the patient who presented pulseless to the emergency department following both blunt and penetrating trauma [8]. In addition to open cardiac massage, cross-clamping of the thoracic aorta is routinely performed to maintain adequate blood flow to the myocardium and brain. Although these maneuvers would improve the rate of successful return of spontaneous circulation (ROSC), removal of aortic cross-clamp often results in significant hemodynamic and metabolic derangements that lead to MOF. Cardiac failure is commonly seen in these cases and often associated with severe myocardial dysfunction caused by multiple mechanisms including ischemic insults and release of inflammatory mediators [9]. In a modern series of EDT at a level 1 trauma center by Moore et al., 35% of patients were rescued from circulatory arrest following EDT, whereas 14% ultimately survived to hospital discharge [10].

Table 12.1 Etiologies of post-injury cardiac failure

Preexisting conditions
• Acute on chronic heart failure (ischemic, non-ischemic)
• Acute myocardial infarction
Trauma-related conditions
• Cardiac injury (blunt rupture, penetrating)
• Blunt cardiac injury/contusion
• Post-cardiac arrest (resuscitative thoracotomy, cross-clamping of the thoracic aorta)
• Air embolism to the coronary artery
• Traumatic brain injury, spinal cord injury (neurogenic cardiomyopathy)
• Status post-pneumonectomy
Other conditions
• Massive pulmonary embolism
• Dysrhythmia
• Systemic inflammatory response (often associated with infection)

Although rarely seen, acute onset of right heart failure in patients undergoing total pneumonectomy for high-grade lung injuries has been reported in previous case series [11]. Aside from uncontrollable hemorrhage and pulmonary infectious complications, high mortality following pneumonectomy is also likely attributed to postoperative acute right heart failure [12]. Bronchopulmonary vein fistula secondary to thoracic trauma, often penetrating injury to the lung, can lead to air embolism of the coronary artery system [13] (Fig. 12.1). Sudden onset of cardiac collapse can be seen following endotracheal intubation with positive ventilation. Another rare clinical entity related to post-injury cardiac failure is known as neurogenic cardiomyopathy or neurogenic cardiac injury in patients with traumatic brain injury [14]. While its mechanism remains unclear, it is proposed that cardiac injury is caused by stress-induced catecholamine release [15].

In severely injured patient, the systemic inflammatory response syndrome (SIRS) is known to be caused by the release of endogenous factors due to significant tissue injury and hemorrhage [16]. SIRS and resultant immune system dysfunction are associated with an increased risk of infectious complications, and this "second hit" further aggravates a vicious cycle of MOF [17]. It has been proposed that myocardial injury caused by these inflammatory mediators often present with an increased troponin level, even in patients without preexisting cardiac dysfunction or mechanical cardiac trauma.

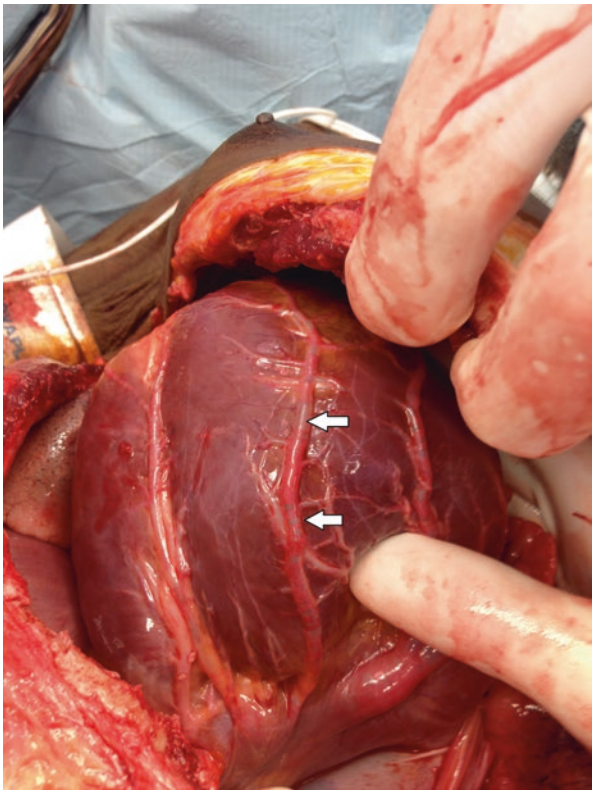


Fig. 12.1 Air embolism to the coronary veins with multiple air bubbles seen (arrows). Source: Demetriades D, Inaba K, Velmahos G. Atlas of Surgical Techniques in Trauma, 2nd edition. Cambridge University Press: 2020

12.3 Clinical Signs and Symptoms

Patients with cardiac failure in the early post-injury period usually sustain multisystem trauma with high injury burden [2]. Upon admission to the ICU, patients are often intubated and sedated while resuscitation being still ongoing. Furthermore, these patients often develop concurrent organ injuries (e.g. acute kidney injury, acute respiratory distress syndrome: ARDS) as a result of inadequate perfusions to end organs and SIRS [1]. Therefore, symptoms commonly seen in different stages of heart failure (e.g. dyspnea on exertion, fatigue) are rarely appreciated, or even if the symptoms are present, they may not be caused by heart failure. Hypovolemic shock due to hemorrhage is the most common cause of circulatory shock during the immediate post-injury period. Cardiogenic shock should also be considered in cases with persistent hypotension (systolic blood pressure <90 mmHg) with/without vasopressor support and evidence of endo-organ damage despite appropriate hemorrhage control and resuscitation.

12.4 Diagnostic Workup

The detailed information regarding patient's comorbid conditions and medication list should be obtained as soon as possible, ideally during the initial resuscitation period in the emergency department. However, it is often challenging to confirm with the patient who presented with altered mental status. If the patient has a known history of chronic heart failure, it is crucial to obtain additional information regarding the etiologies (e.g. ischemic, non-ischemic) and baseline cardiac function (e.g. exercise tolerance, result of recent echocardiography).

In patients presenting with penetrating wounds to the chest and upper abdomen, an evaluation for cardiac injury should be a part of the initial trauma assessment. Of note, cardiac injury can be associated with external penetrating wounds outside of the classic "cardiac box," particularly following gunshot injuries [18]. The patient can be asymptomatic and hemodynamically stable, thus routine use of FAST in the trauma bay enables to identify those with subclinical cardiac injury with pericardial effusion (hemopericardium) deteriorating into extremis. While the reported sensitivity of pericardial FAST reaches nearly 100%, the result of FAST can be falsely negative in cases with violated pericardium. In these cases, the patient is found to have a negative FAST with large amount of hemothorax, often in the left chest [19, 20]. The utility of laboratory tests for the diagnosis of cardiac injury remains controversial; however, a normal cardiac enzyme (e.g. troponin) level and electrocardiography (ECG) can be used to rule out clinically significant blunt cardiac injuries [21].

Despite the comprehensive workup without any evidence of ongoing blood loss, if the patient remains hemodynamically unstable, cardiogenic shock should be a part of differential diagnoses. As shown in Table 12.1, trauma-related etiologies including cardiac injury need to be ruled out first. As previously described, a combination of negative FAST, chest radiography, troponin level, and ECG can reliably

rule out blunt and penetrating cardiac injuries. If the results of ECG and troponin suggest blunt cardiac injury or acute myocardial ischemia, further workup should include echocardiography for the evaluation of: (1) intracardiac pathology (e.g. valvular disease), (2) contractility (e.g. ejection fraction), (3) volume status (e.g. inferior vena cava and ventricular size), and (4) further evaluation of pericardial effusion. While transthoracic echocardiography (TTE) is often chosen as it can be readily performed at bedside, appropriate visualization of the heart can be challenging due to associated injuries such as multiple rib fractures and pneumothorax, body habitus, severe pain, particularly in patients with severe thoracic injuries. Transesophageal echocardiography (TEE) can be considered as an alternative in those cases. Although it is rarely seen in the acute trauma setting, when acute coronary syndrome is suspected based on ECG findings, the indication for an emergency percutaneous coronary intervention (PCI) should be discussed with interventional cardiologists.

In most cases with suspected cardiogenic shock, the patient is also being resuscitated with blood products simultaneously, while diagnostic workup for hemorrhagic shock is still ongoing. Furthermore, those with multisystem trauma often undergo emergent surgical or endovascular interventions before the workup is completed [22]. The use of vasopressors/inotropes in these setting can mask ongoing hemorrhage and delay the definitive hemorrhagic control. Real-time monitoring with point-of-care echocardiography or intraoperative transthoracic echography may be useful to guide the resuscitation during hemorrhage control procedures in the operating room or interventional radiology suite.

12.5 Management in the Intensive Care Unit

12.5.1 Postoperative Management of Cardiac Trauma

The large majority of patients with cardiac injuries that survive postoperatively to the ICU should have undergone a primary repair of cardiac injuries. It is extremely rare that those patients were placed on cardiopulmonary bypass intraoperatively for coronary or valvular procedures [23]. However, the patient is often admitted to the ICU after cardiac repair while receiving hemostatic resuscitation with blood products and inotrope/vasopressor support. As the diagnostic workup is often not completed preoperatively, hemodynamic instability can be secondary to undiagnosed hemorrhage from associated injuries in the cavities that were not evaluated intraoperatively (abdomen, retroperitoneum) [22]. In addition, the output from different types of surgical drains should be carefully monitored for any signs of ongoing hemorrhage (e.g. pericardial drain, thoracostomy tube, negative pressure therapy device). Of note, a patient who underwent cardiac procedures can develop cardiac tamponade postoperatively despite the pericardial space being drained with surgical drains. In these cases, the pericardial drain is not functioning appropriately, and its output is usually low despite ongoing bleeding into the pericardial space. An emergent bedside ultrasound is the diagnostic modality of choice and if it is positive, an emergent decompression of the pericardial space is required. A routine

echocardiography is recommended to evaluate any injury to internal structures of the heart including valves and septum [24].

12.5.2 Evaluation and Management of Cardiogenic Shock

While other causes of circulatory shock are evaluated, it is important to assess cardiac function for the patient with persistent hemodynamic instability despite ongoing resuscitation from the emergency department to the ICU. This can be accomplished using different types of assessment tools [25]. In recent years, point-of-care TTE (ECHO) at bedside has been utilized more frequently in the trauma setting and proven to be accurate and effective for the assessment and guidance of treatment in unstable patients in the emergency department and surgical ICU [26, 27]. The data obtained include: (1) ventricular function (e.g. ejection fraction), (2) motion abnormalities, (3) valvular disease/dysfunction, (4) right heart function and pressure, (5) others (e.g. pericardial effusion). While these studies are often performed by ultrasound technicians from cardiology or radiology, an increasing number of trauma surgeons and surgical residents/fellows are now trained to perform ECHO with comparable quality of images to be used for evaluation [28]. Furthermore, ECHO can be used not only for the initial evaluation of volume status and cardiac function, but also for serial assessment of the interventions based on the data obtained.

The management of cardiogenic shock should be tailored based on assessments developed with the results of diagnostic tests. Although the use of vasopressors and/or inotropes might be required for cardiac dysfunction, it should be reminded that associated hemorrhagic shock is common, especially during the immediate post-injury phase. In contrast, cardiac dysfunction in the post-resuscitation phase can be a part of MOF caused by PICS. Pharmacologic measures to support cardiac function should be guided by the data obtained with hemodynamic monitoring such as echocardiography or pulmonary artery catheter. Proposed strategies to mitigate the risk of inflammation-mediated organ failure after trauma include: (1) modulate SIRS, (2) stimulate natural immunity, and (3) prevent microbial proliferation, although further research is still warranted [16].

For cardiogenic shock, often associated with pulmonary failure refractory to conventional treatments including optimizing volume status and non-invasive cardiopulmonary support, mechanical support of cardiopulmonary system may be indicated. Intra-aortic balloon pump (IABP) can be a useful adjunct in patent with refractory cardiogenic shock. IABP can improve cardiac output by increasing blood flow to the coronary arteries and decreasing afterload. IABP is contraindicated in patients with aortic injury. In the case with persistent arrhythmia causing hemodynamic instability following open cardiac procedures, temporary epicardial pacing can be considered to improve cardiac function (Fig. 12.2a, b).

Along with other indications, the use of extracorporeal life support (ECLS) in trauma patients has been proposed and there are several studies showing favorable results associated with the use of ECLS over the last decades (Fig. 12.3) [29, 30].

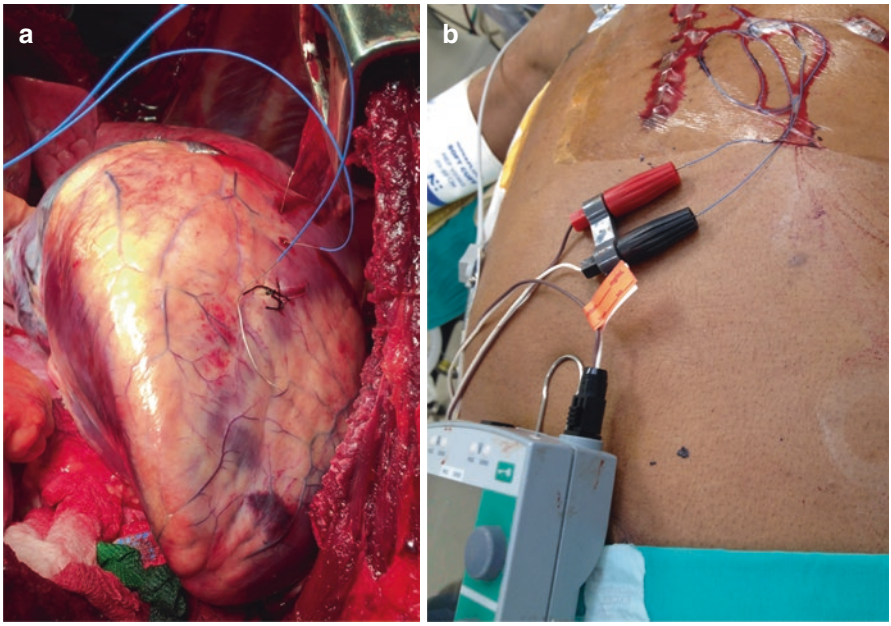


Fig. 12.2 (**a**, **b**) Epicardial pacing of a patient who underwent resuscitative thoracotomy following traumatic cardiac arrest. Source: Demetriades D, Inaba K, Velmahos G. Atlas of Surgical Techniques in Trauma, second edition. Cambridge University Press: 2020

Fig. 12.3 Veno-arterial ECMO for right heart failure following traumatic pneumonectomy. *ECMO* extracorporeal membrane oxygenation

An initial experience in the use of ECLS by Lin et al. showed that the overall hospital survival rate of 51.6% in 43 patients who underwent extracorporeal membrane oxygenation (ECMO) for post-traumatic cardiopulmonary failure [29]. Of those who underwent veno-arterial ECMO (VA-ECMO), 41.2% (7/17) survived to hospital discharge. In a retrospective study using the ECLS registry between 1989 and 2016, Swol et al. identified a total of 279 patients undergoing ECLS (<1% of all patients in the ECLS registry) [30]. Of those, 196 patients were managed with

ECLS after 2009. Of note, the large majority of indications were respiratory failure and only 11.5% underwent ECLS for cardiac support. Although the highest survival was observed in the patient who underwent ECLS for respiratory indications (61%), it is important to note that the outcome of trauma patients undergoing ECLS for cardiac support was comparable to the non-trauma patients (50% vs. 41%). ECMO has been also used for trauma patients undergoing resuscitative thoracotomy. Owattanapanich et al. identified 26 patients (0.6% of resuscitative thoracotomies) in the American College of Surgeons Trauma Quality Improvement Program database (2007–2017) that received ECMO within 1 h after resuscitative thoracotomy [31]. Of note, ROSC was achieved in 96% and the mortality rate of ECMO patients was 52%.

12.6 Prognosis

In patients with penetrating cardiac injuries presenting to the emergency department, the overall survival rate was reported to be 36.6% (stab wounds: 68.0%, gunshot wounds: 14.3%) by Asensio et al. at a level 1 trauma center [32]. In contrast, only 16.2% of patients that underwent EDT survived to hospital discharge. While the incidence of blunt cardiac rupture among patients survived to hospital admission is exceedingly low, a retrospective study by Teixeira et al. showed that 11.5% of those with signs of life upon arrival survived to discharge [33]. Trauma patients that developed infectious complications in ICU were more likely to have subsequent cardiac injury [17]. An elevated troponin level in ICU patients with suspected post-injury cardiac failure is shown to be associated with an increased risk of hospital mortality [34].

References

1. Sauaia A, Moore EE, Johnson JL, Chin TL, Banerjee A, Sperry JL, Maier RV, Burlew CC. Temporal trends of postinjury multiple-organ failure: still resource intensive, morbid, and lethal. J Trauma Acute Care Surg. 2014;76(3):582–92.
2. Cole E, Gillespie S, Vulliamy P, Brohi K. Organ Dysfunction in Trauma (ORDIT) study collaborators. multiple organ dysfunction after trauma. Br J Surg. 2020;107(4):402–12.
3. Shepherd JM, Cole E, Brohi K. Contemporary patterns of multiple organ dysfunction in trauma. Shock. 2017;47(4):429–35.
4. Rhee P, Joseph B, Pandit V, Aziz H, Vercruysse G, Kulvatunyou N, Friese RS. Increasing trauma deaths in the United States. Ann Surg. 2014;260(1):13–21.
5. Prin M, Li G. Complications and in-hospital mortality in trauma patients treated in intensive care units in the United States, 2013. Inj Epidemiol. 2016;3(1):18. https://doi.org/10.1186/s40621-016-0084-5.
6. Bell TM, Zarzaur BL. The impact of preexisting comorbidities on failure to rescue outcomes in nonelderly trauma patients. J Trauma Acute Care Surg. 2015;78(2):312–7.
7. Teixeira PG, Georgiou C, Inaba K, Dubose J, Plurad D, Chan LS, Toms C, Noguchi TT, Demetriades D. Blunt cardiac trauma: lessons learned from the medical examiner. J Trauma. 2009;67(6):1259–64.

8. Seamon MJ, Haut ER, Van Arendonk K, Barbosa RR, Chiu WC, Dente CJ, Fox N, Jawa RS, Khwaja K, Lee JK, Magnotti LJ, Mayglothling JA, McDonald AA, Rowell S, To KB, Falck-Ytter Y, Rhee P. An evidence-based approach to patient selection for emergency department thoracotomy: a practice management guideline from the Eastern Association for the Surgery of trauma. J Trauma Acute Care Surg. 2015;79(1):159–73.
9. Kralovich KA, Morris DC, Dereczyk BE, Simonetti V, Williams M, Rivers EP, Karmy-Jones R. Hemodynamic effects of aortic occlusion during hemorrhagic shock and cardiac arrest. J Trauma. 1997;42(6):1023–8.
10. Moore HB, Moore EE, Burlew CC, Biffl WL, Pieracci FM, Barnett CC, Bensard DD, Jurkovich GJ, Fox CJ, Sauaia A. Establishing benchmarks for resuscitation of traumatic circulatory arrest: success-to-rescue and survival among 1,708 patients. J Am Coll Surg. 2016;223(1):42–50.
11. Baumgartner F, Omari B, Lee J, Bleiweis M, Snyder R, Robertson J, Sheppard B, Milliken J. Survival after trauma pneumonectomy: the pathophysiologic balance of shock resuscitation with right heart failure. Am Surg. 1996;62(11):967–72.
12. Matsushima K, Aiolfi A, Park C, Rosen D, Strumwasser A, Benjamin E, Inaba K, Demetriades D. Surgical outcomes after trauma pneumonectomy: revisited. J Trauma Acute Care Surg. 2017;82(5):927–32.
13. Campbell PR, Kerridge R. Fatal traumatic air embolism following a stab wound to the chest. Aust N Z J Surg. 1993;63(4):307–9.
14. Hasanin A, Kamal A, Amin S, Zakaria D, El Sayed R, Mahmoud K, Mukhtar A. Incidence and outcome of cardiac injury in patients with severe head trauma. Scand J Trauma Resusc Emerg Med. 2016;27(24):58.
15. Naredi S, Lambert G, Edén E, Zäll S, Runnerstam M, Rydenhag B, Friberg P. Increased sympathetic nervous activity in patients with nontraumatic subarachnoid hemorrhage. Stroke. 2000;31(4):901–6.
16. Lord JM, Midwinter MJ, Chen YF, Belli A, Brohi K, Kovacs EJ, Koenderman L, Kubes P, Lilford RJ. The systemic immune response to trauma: an overview of pathophysiology and treatment. Lancet. 2014;384(9952):1455–65.
17. Monaghan SF, Adams CA Jr, Stephen AH, Connolly MD, Gregg SC, Machan JT, Cioffi WG, Heffernan DS. Infections after trauma are associated with subsequent cardiac injury. J Trauma Acute Care Surg. 2012;73(5):1079–84.
18. Jhunjhunwala R, Mina MJ, Roger EI, Dente CJ, Heninger M, Carr JS, Dougherty SD, Gelbard RB, Nicholas JM, Wyrzykowski AD, Feliciano DV, Morse BC. Reassessing the cardiac box: a comprehensive evaluation of the relationship between thoracic gunshot wounds and cardiac injury. J Trauma Acute Care Surg. 2017;83(3):349–55.
19. Rozycki GS, Ballard RB, Feliciano DV, Schmidt JA, Pennington SD. Surgeon-performed ultrasound for the assessment of truncal injuries: lessons learned from 1540 patients. Ann Surg. 1998;228(4):557–67.
20. Ball CG, Williams BH, Wyrzykowski AD, Nicholas JM, Rozycki GS, Feliciano DV. A caveat to the performance of pericardial ultrasound in patients with penetrating cardiac wounds. J Trauma. 2009;67(5):1123–4.
21. Velmahos GC, Karaiskakis M, Salim A, Toutouzas KG, Murray J, Asensio J, Demetriades D. Normal electrocardiography and serum troponin I levels preclude the presence of clinically significant blunt cardiac injury. J Trauma. 2003;54(1):45–50.
22. Matsushima K, Inaba K, Dollbaum R, Khor D, Jhaveri V, Jimenez O, Strumwasser A, Demetriades D. The role of computed tomography after emergent trauma operation. J Surg Res. 2016;206(2):286–91.
23. Asensio JA, Berne JD, Demetriades D, Chan L, Murray J, Falabella A, Gomez H, Chahwan S, Velmahos G, Cornwell EE, Belzberg H, Shoemaker W, Berne TV. One hundred five penetrating cardiac injuries: a 2-year prospective evaluation. J Trauma. 1998;44(6):1073–82.
24. Tang AL, Inaba K, Branco BC, Oliver M, Bukur M, Salim A, Rhee P, Herrold J, Demetriades D. Postdischarge complications after penetrating cardiac injury: a survivable injury with a high postdischarge complication rate. Arch Surg. 2011;146(9):1061–6.

25. Strumwasser A, Frankel H, Murthi S, Clark D, Kirton O. American Association for the Surgery of Trauma Committee on critical care. Hemodynamic monitoring of the injured patient: from central venous pressure to focused echocardiography. J Trauma Acute Care Surg. 2016;80(3):499–510.
26. Ferrada P, Evans D, Wolfe L, Anand RJ, Vanguri P, Mayglothling J, Whelan J, Malhotra A, Goldberg S, Duane T, Aboutanos M, Ivatury RR. Findings of a randomized controlled trial using limited transthoracic echocardiogram (LTTE) as a hemodynamic monitoring tool in the trauma bay. J Trauma Acute Care Surg. 2014;76(1):31–7.
27. Ferrada P, Murthi S, Anand RJ, Bochicchio GV, Scalea T. Transthoracic focused rapid echocardiographic examination: real-time evaluation of fluid status in critically ill trauma patients. J Trauma. 2011;70(1):56–62.
28. Ferrada P, Anand RJ, Whelan J, Aboutanos MA, Duane T, Malhotra A, Ivatury R. Limited transthoracic echocardiogram: so easy any trauma attending can do it. J Trauma. 2011;71(5):1327–31.
29. Lin CY, Tsai FC, Lee HA, Tseng YH. Extracorporeal membrane oxygenation support in post-traumatic cardiopulmonary failure: a 10-year single institutional experience. Medicine (Baltimore). 2017;96(6):e6067.
30. Swol J, Brodie D, Napolitano L, Park PK, Thiagarajan R, Barbaro RP, Lorusso R, McMullan D, Cavarocchi N, Hssain AA, Rycus P, Zonies D. Extracorporeal Life Support Organization (ELSO). Indications and outcomes of extracorporeal life support in trauma patients. J Trauma Acute Care Surg. 2018;84(6):831–7.
31. Owattanapanich N, Inaba K, Allen B, Lewis M, Henry R, Clark D, Matsushima K, Strumwasser A. Extracorporeal membrane oxygenation may improve outcomes after resuscitative thoracotomy: a national trauma data bank analysis. Am Surg. 2021;87(10):1565–8.
32. Asensio JA, Murray J, Demetriades D, Berne J, Cornwell E, Velmahos G, Gomez H, Berne TV. Penetrating cardiac injuries: a prospective study of variables predicting outcomes. J Am Coll Surg. 1998;186(1):24–34.
33. Teixeira PG, Inaba K, Oncel D, DuBose J, Chan L, Rhee P, Salim A, Browder T, Brown C, Demetriades D. Blunt cardiac rupture: a 5-year NTDB analysis. J Trauma. 2009;67(4):788–91.
34. Martin M, Mullenix P, Rhee P, Belzberg H, Demetriades D, Salim A. Troponin increases in the critically injured patient: mechanical trauma or physiologic stress? J Trauma. 2005;59(5):1086–91.

13 Liver Dysfunction and Failure: Clinical Presentation, Pathophysiology, and Management

Osamu Yoshino

13.1 Historical Perspective and Definition

Multiple organ failure (MOF) remains a leading cause of late trauma death. Since the term MOF was coined by Eiseman and colleagues in 1977, extensive efforts have been made to understand this condition [1, 2]. Postinjury liver failure is a part of MOF with dramatic clinical features that can result in death. It is a temporary or permanent reactive sequence of reversible or irreversible hormonal, inflammatory, and immunological alterations during severe injury and subsequent prolonged recovery. One of the most commonly validated definitions of MOF, the Denver score, uses four organ score systems: cardiovascular, hepatic, renal, and pulmonary function (Table 13.1). In the Sequential Organ Assessment Score (SOFA) and Marshall Multiple Organ Dysfunction Score (MODS), platelet counts and serum bilirubin levels are used for liver function assessment [3]. The scores' sensitivity and specificity are lower for the liver than other organs [3]. This low diagnostic value is probably due to the characteristics of serum bilirubin values, which tend to be influenced by extrahepatic factors, including transfusion, hemolysis, and infection. Platelet count can be significantly affected by initial hemorrhage and resuscitation, as well as fluid status. Nevertheless, we define liver failure according to the Denver score's definition (bilirubin >137 μmol/L) in this chapter (Table 13.1).

Abnormal liver test results—such as hyperbilirubinemia and elevated gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels—are commonly observed among critically ill patients in the ICU [12]. The exact etiology underlying

O. Yoshino (✉)
Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Carolinas Medical Center, Atrium Health, Charlotte, NC, USA
e-mail: Osamu.Yoshino@atriumhealth.org

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_13

Table 13.1 Summary of the Denver Score, SOFA, and MODS

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Denver score					
$PaO_2/FiOs$ (mmHg)	>208	208–165	165–83	<83	
Serum bilirubin (μmol/L)	<34	34–68	69–137	>137	
Serum creatinine (μmol/L)	<159	160–210	211–420	>420	
Inotropes requirement	No inotrope	1 inotrope at a small dose	Any inotrope at moderate dose or >1 agent at small dose	Any inotrope at large dose or >1 agent at moderate dose	
SOFA					
$PaO_2/FiOs$ (mmHg)	>400	<400	<300	<200	<100
Platelet count (10^3/μL)	>150	<15	<100	<50	<20
Serum bilirubin (μmol/L)	<20	20–32	33–101	102–204	>204
Serum creatinine (μmol/L)	<110	110–170	171–299	300–440	>440
Inotropes requirement (ug/kg/min)	No hypotension	MAP <70 mmHg	Dopamine <5 or any Dobutamine	Dopamine >5 or Adrenaline <0.1 or Noradrenaline <0.1	Dopamine >15 or Adrenaline >0.1 or Noradrenaline >0.1
GCS	15	13–14	10–12	6–9	<6
MODS					
$PaO_2/FiOs$ (mmHg)	>300	226–300	151–225	76–150	<76
Platelet count (10^3/μL)	>120	81–120	51–80	21–50	<21
Serum bilirubin (μmol/L)	<21	21–60	61–120	121–240	>240
Serum creatinine (μmol/L)	<101	101–200	201–350	351–500	>500
PAR	<10.1	10.1–15.0	15.1–20.0	20.1–30.0	>30.0
GCS	15	13–14	10–12	6–9	<6

PAR = Heart Rate × Central Venous Pressure/Mean Arterial Blood Pressure

the alterations in the liver enzymes described above is not fully understood. Whether these abnormal values truly reflect liver dysfunction or are simply consequences of physiological stresses remains debated. Cholestasis, for example, is commonly observed in sepsis and can be observed as an elevation of serum bilirubin, GGT and ALP, or less frequently AST and ALT. Nevertheless, the association between abnormal serum bilirubin and liver failure is poorly understood [13].

13.2 Epidemiology

Liver failure is a rare postinjury organ dysfunction with a reported incidence between 0.14% and 4.9% among severely injured patients (ISS ≥ 16) and up to 10% among patients with MOF [2, 14, 15], depending on the definition applied. Postinjury MOF is a bimodal phenomenon comprising early MOF, with an onset within 48 h after the initial injury, and late MOF, with an onset ≥48 h after the initial injury [14]. Liver failure is more prevalent in late MOF than early MOF; however, whether this failure occurs because the liver is more vulnerable to a second hit such, as infection, or is a consequence of series of physiological insults remains unclear [14, 16]. Because the incidence of MOF has been significantly decreasing, few patients currently experience postinjury liver failure [2, 17].

13.3 Pathophysiology of Postinjury Liver Failure

13.3.1 Shock Liver: Initial Ischemia and Reperfusion Injury in the Liver

One proposed mechanism of postinjury MOF is the "two-hit theory" [18, 19]. Early liver failure may be due to pre-existing liver disease, such as cirrhosis and nonalcoholic steatohepatitis, or primary or secondary liver injury, such as shock liver due to massive hemorrhagic shock [20]. Pre-existing liver disease can rapidly worsen after significant injury, even with resuscitation. The patients tend to show abnormal coagulation functions including hypercoagulation and hypocoagulation, owing to an imbalance in coagulation factors, a lack of platelets and its function. The diseased liver tends to be vulnerable to external stress, such as hemorrhage, associated fluid resuscitation and infection, and thus is associated with high mortality [21].

Ischemia/reperfusion injury (IR injury) is the main contributor to postinjury liver failure [22, 23]. IR injury has been reported in many clinical settings, including hemorrhagic shock, trauma, liver surgery, liver transplantation, and sepsis [24, 25]. The liver appears to tolerate ischemia to some extent, as has been well demonstrated in liver surgery [26, 27]. Most of the knowledge in regard to the alterations in liver function and injury from IR injury comes from animal experiments.

The main factors contributing to liver injury appear to be active vasoconstriction and cell entrapment in sinusoids, leading to obstructive microcirculation and immunological dysfunction of hepatic sinusoids resulting in uncontrolled inflammation

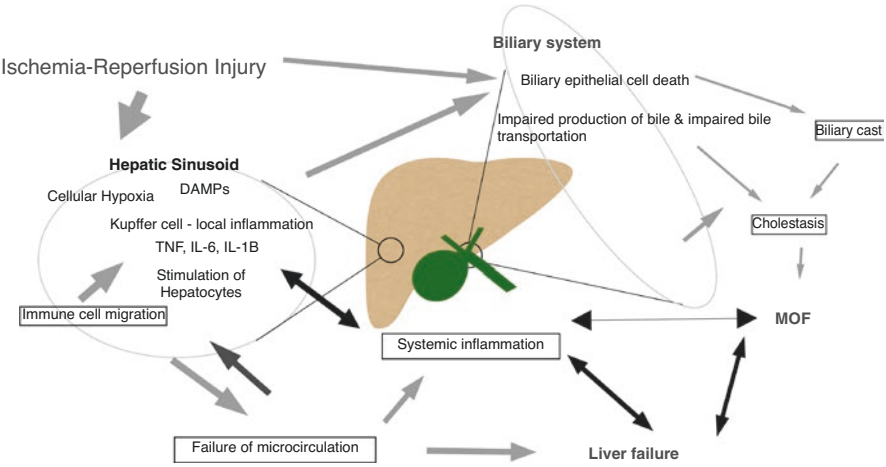


Fig. 13.1 Pathophysiology of postinjury liver failure. Significant local inflammation due to ischemia and reperfusion leads to failure of microcirculation in liver, which stimulate systemic inflammation [4]. Kupffer cells appear to play in an important role in this inflammatory cascade [5–7]

[4]. During the initial ischemic phase, reactive oxygen species (ROS) are produced, and the liver and other distant organs experience oxidative stress [28]. In the liver, ROS activate Kupffer cells, thereby stimulating further formation of ROS and cytokines. In the sinusoids, vasoconstriction occurs because of an imbalance between endothelin-1 and nitric oxide [5, 6]. Excessive inflammation during reperfusion occurs immediately after ischemia and is recognized as a key mechanism underlying subsequent liver failure [29]. Increased production of interleukin-1b and tumor necrosis factor-α (TNF-α) leads to the migration of neutrophils, macrophages, T lymphocytes, and platelets into the liver. In hepatocytes, surface adhesion molecules (intracellular cell adhesion molecule and vascular cell adhesion molecule) are significantly expressed, thus resulting in endothelial and inflammatory cell adhesion in the constricted sinusoids. Consequently, microcirculation failure occurs because of endothelial cell swelling with mechanical obstruction due to inflammatory cells as well as microthrombi [30, 31]. Local inflammation in the sinusoids with microvasculature failure further stimulates inflammation through the production of granulocyte-macrophage colony-stimulating factor, interferon gamma, and TNF-β, which amplify Kupffer cells and increase cytokine release, thus leading to a self-propagating negative cascade [7]. Interestingly apoptosis or necrosis, which is an ultimate consequence of excessive inflammation, is not a characteristic of postinjury liver failure and further work is warranted to deepen the understanding of the pathophysiology of shock liver (Fig. 13.1).

13.3.2 Sepsis and Its Immune Reactions in Liver Failure

Infection and sepsis constitute significant physiological insults. Sepsis, as a second hit, is associated with postinjury MOF and subsequent mortality. The liver, in

addition to the gut, is now recognized as a second line of defense in eliminating bacteria and bacterial products [32]. The gut and surrounding immune system play a pivotal role in preventing the translocation of intestinal bacteria [33]. This complex system is imperative to inhibit and eliminate bacteria and its products. Patients with cirrhosis, for example, have an increased risk of bacterial infections, which commonly originate from the intestine [34, 35].

The liver accepts the entire bloodstream from the intestines and therefore is an important part of immunological defense. The entire portal bloodstream, which can potentially be contaminated with bacteria, is filtered through the liver. Immune surveillance and bacterial elimination occur mainly in the hepatic sinusoids; this process is also called microcirculation of the liver [36]. In the case of bacterial translocation via the portal vein, immune reactions between bacteria and immune cells, including hepatic sinusoid endothelial cells, hepatic stellate cells, Kupffer cells, and migrated immune cells, induce inflammatory responses. This local inflammation in the hepatic sinusoids is essential to clear bacteria and associated toxins. One study has demonstrated that >60% of intravenously injected bacteria are trapped in the liver within 10 minutes [37]. Hepatic macrophages can directly eliminate invasion by some bacteria and otherwise activate systemic immune responses including migration of leukocytes, neutrophils, and macrophages. Neutrophils provide immune protection through phagocytosis and neutrophil extracellular traps (NETs), although NETs appear to impair microcirculation and thus lead to mild ischemic hepatic injury [38]. Interestingly, these immunological defense mechanisms might be sufficiently sophisticated to switch their own reactions between immunological tolerance via regulatory T cell responses and opposite cytotoxic T cell responses [6]. Nevertheless, the immune response from the liver is a double-edged sword that may contribute to organ damage if its own inflammatory responses are excessive [37].

13.3.3 Cholestasis

Prolonged cholestasis is observed after the initial phase of liver failure [39, 40] and may occur through two potential mechanisms: impaired bile formation at the hepatocellular level or altered bile transportation. In a laboratory study, proinflammatory cytokines and mediators have been found to downregulate the expression of members of the hepatocellular transport system, such as the canalicular bile-salt export pump and basolateral sodium taurocholate cotransporter [41, 42].

Impaired bile flow has been relatively less investigated and is not well understood. Cholangiocytes can provoke more inflammation through secretion of cytokines such as TNF and IFNγ, thus leading to periductular inflammation, which inhibits chloride and bicarbonate ion transportation and leads to impaired bile flow [43].

Increased serum bile acid concentrations in cholestatic conditions negatively affect organ function, thereby resulting in impaired glucose and lipid metabolism, impaired renal function, immunosuppression, and vasodilatation. High bilirubinemia in patients with liver failure is strongly prognostic for short-term mortality [40, 44].

13.3.4 Secondary Sclerosing Cholangitis

Secondary sclerosing cholangitis is a rare complication in patients with postinjury MOF. It is characterized by initial ischemic-reperfusion injury, subsequent inflammation, and fibrotic destruction of the bile ducts [45]. One study has reported that all five patients examined experienced major trauma and subsequently showed consistently elevated bilirubin and GGT, and all developed cirrhosis and subsequently died [46]. Cholangiography demonstrated multifocal strictures and dilatations. Although the etiology is not yet clearly defined, IR injury might play a pivotal role in inflammation of biliary epithelial cells, which are exceptionally vulnerable to hypoxic injury.

13.3.5 Effects of Liver Failure on Other Organ Systems

Postinjury liver failure is often associated with other organ injuries. Respiratory failure is common in the setting of severe liver failure with ventilatory support. Patients are vulnerable to nosocomial infection such as ventilation-associated pneumonia, bacterial translocation, or intraabdominal infection. Abnormally increased intra-pulmonary venous-arterial shunt is a unique pathophysiology in the context of hepatopulmonary syndrome [8], although its incidence in postinjury MOF has not been described elsewhere (Fig. 13.2).

Hepatorenal syndrome may be explained by fluid and electrolyte imbalance, decreased cardiac output as part of MOF, increased intrahepatic vascular resistance, and inappropriate splanchnic vasodilation secondary to various factors, including disruption of arginine synthesis [9]. Nevertheless, most cases of renal failure in a setting of postinjury MOF are likely to be due to other causes, such as hypovolemic shock leading to acute renal injury [47].

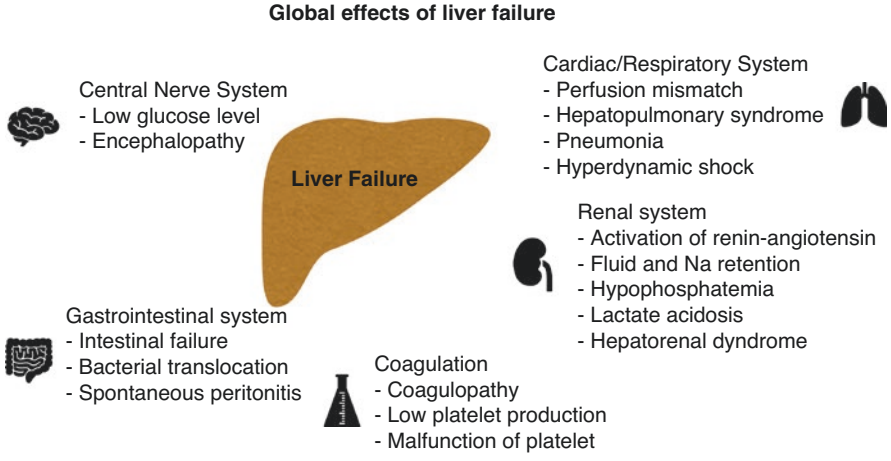


Fig. 13.2 Global effects of liver failure [7–11]

13.4 Clinical Presentation, Management, and Prognosis

13.4.1 Diagnosis

Diagnosis of early liver failure can be challenging because of the influence of many factors including pre-existing liver disease, resuscitation with blood transfusion, intraabdominal injury, and infection. Resuscitation must be completed, because early MOF with liver failure is extreme rare, and such a clinical presentation might reflect inadequate resuscitation. Hyperbilirubinemia must be investigated cautiously in a timely manner. Common etiologies such as acalculous cholecystitis secondary to ischemia and choledocholelithiasis must be excluded in the setting of abnormally elevated liver enzymes. Bile duct obstruction due to duodenal hematoma has been well reported in the literature [48]. Doppler ultrasound and cross-sectional imaging can provide useful information on bile duct anatomy, liver vasculature patency (e.g., portal vein thrombosis due to blunt trauma), and any primary hepatic pathology. Occasional infections including hepatitis, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and HIV must be routinely verified. Other laboratory tests include toxicology screening, hepatitis serology screening, autoimmune markers such as anti-nuclear antibody and anti-smooth muscle antibody, serum copper levels, and ammonia (Table 13.2).

13.4.2 Early Liver Failure

Postinjury liver failure in the early phase is due to severe ischemia and reperfusion, particularly among patients with prolonged hypovolemic shock with massive transfusion or cardiac arrest [20]. These patients often simultaneously develop other

Table 13.2 Screening laboratory test for liver failure

Hematology	Complete blood count, prothrombin time, and INR factor V activity, factor VII activity
Biochemistry	Liver function test (AST, ALT, GGT, indirect and direct bilirubin), albumin, electrolytes (Na, K, Ur, creatinine, Mg, and PO_4), glucose, ammonia
	Amylase and lipase
Arterial blood gas	pO_2, pCO_2, base excess, lactic acid
Blood group	Blood type
Toxicology	Serum acetaminophen level, serum copper level, iron study, and toxicology screening
Hepatitis screening	Anti-HAV IgM, HBsAg, anti-HBcIgM and anti-hepatitis E virus
Autoimmune markers	Anti-nuclear antibody, anti-smooth muscle antibody, liver and kidney microsomal antibody, immunoglobulin level
Infection	Epstein–Barr virus, herpes simplex virus, and HIV

AST aspartate transaminase, *ALT* alanine aminotransferase, *GGT* gamma-glutamyl transpeptidase, *HAV* hepatitis type A virus, *HBsAg* Anti-hepatitis B Surface Allergy, *HBcIgM* hepatitis B core immunoglobulin type M antibodies

organ failure, such as circulatory and respiratory failure. Ongoing fluid resuscitation and inotropic support are required with ventilator support. Laboratory patterns in early liver failure, such as elevation of ALT and AST rather than ALP and GGT, represent hepatocellular damage. Management for early liver failure is the best supportive care, with optimization of fluid resuscitation. Clinicians must be aware of several principles of fluid resuscitation: (1) minimization of the use of crystalloid; (2) early hemostasis with damage control surgery to minimize second physiological insults; (3) early administration of blood products; (4) judicious use of blood products; (5) if intraabdominal injury requires intervention, monitoring of intraabdominal pressure to avoid abdominal compartment syndrome; and (6) correct coagulopathy. Management for early liver failure is a part of the initial resuscitation.

13.4.3 Late Liver Failure

Late presentation of liver failure is more complex and is frequently associated with early moderate physiological insults with a subsequent second hit, such as secondary surgery, infection or abdominal compartment syndrome. Given that the treatment is largely supportive, preventive measures including optimization of fluid resuscitation, carefully considered secondary interventions with a damage control strategy and minimization of complications, such as sepsis and abdominal compartment syndrome, are more practically beneficial than treating postinjury liver failure.

13.4.4 Infection

Sepsis has a pivotal role in the development of liver failure. Infection control among postinjury patients is difficult because of their immunosuppressed status [49]. Secondary infection leading to sepsis is frequently observed as a second hit in patients with postinjury MOF.

Aggressive source control, particularly for intraabdominal infection, including radiological and surgical drainage, is essential together with the use of broad spectrum antibiotics with antifungal agents.

13.4.5 Supportive Multiorgan Care

After liver failure develops, patient management is challenging, and the mortality rate may reach 40% [17, 50]. Liver failure must be managed to prevent further complications and provide the best environment possible for liver regeneration. A multiorgan approach is key to managing postinjury liver failure. Respiratory support is often required because of altered consciousness, although respiratory failure is commonly observed in postinjury MOF [2, 50]. The respiratory failure may be due to primary torso injury, such as multiple rib fractures, pulmonary contusion and

pneumohemothorax, or to hospital-acquired pneumonia. Protective lung ventilation should be used to prevent further lung injury, because positive pressure ventilation can cause ventilator-induced lung injury or exacerbate existing lung damage [51].

Adrenal insufficiency after trauma is relatively common and should be actively investigated in patients requiring vasopressors. Although the benefits of steroids in severely injured patients remain debatable, if clear evidence of adrenal insufficiency exists, the supplementary administration of steroids must be strongly considered [52, 53].

Optimization of fluid balance with euvolemia is essential. Aggressive use of diuretics may be required, and restriction of sodium intake is important. Concomitant infection of ascites can readily occur if ascites accumulate. In particular, intraabdominal injury and surgery can complicate the management.

13.4.6 Intracranial Hypertension

If the liver failure is severe, intracranial pressure (ICP) must be continuously monitored [54]. ICP increases, thereby influencing cell integrity in the brain and leading to encephalopathy. The normal ICP in adults is below 15 mmHg, and intracranial hypertension (ICH) is defined by a sustained pressure of 20 mmHg or above [55]. ICH in liver failure occurs because of the rapid development of cerebral edema. Two hypotheses may potentially explain this observation: (1) loss of cerebral autoregulation leading to tissue edema, circulation of secondary inflammatory mediators, and disruption of the blood–brain barrier and (2) ammonia's effects on osmotically active glutamine by astrocytes leading to cerebral edema [10]. Strategies to manage ICH have been extensively investigated in the neurosurgical and intensive care settings, including infection control, fluid and electrolyte management, glycemic control, tight control of respiratory indices, head elevation, and possibly hypothermia and osmotherapy with mannitol or hypertonic saline [56]. The use of hypertonic saline requires careful attention. If serum sodium levels change rapidly, myelinolysis may cause irreversible injury to the brain [57]. Aggressive use of lactulose is essential, and continuous hemofiltration to minimize ammonia production may be considered, because serum ammonia levels correlate with the severity of hepatic encephalopathy [58].

13.4.7 Renal Management

Acute impairment of renal function in a setting of liver failure, as diagnosed by an increase in serum creatinine, is underestimated. Impairment of the hepatic production of creatinine, significant catabolic status, and inaccurate calorimetric methods in the presence of elevated serum bilirubin make its diagnosis challenging [59]. However, continuous monitoring of urinary output and serum/urine sodium and creatinine levels is inexpensive and diagnostic. Continuously maintaining urinary output, electrolytes, and fluid balance is critical. Drainage of ascites, if intraabdominal

hypertension is suspected, is essential. Because of sodium retention, restriction of sodium intake and fluids, together with daily correction of serum electrolytes, is important. Aggressive use of diuretics is often required [59]. Continuous hemofiltration or dialysis is useful for fluid management in the setting of concomitant liver failure, because these modalities can also remove ammonia [60].

13.4.8 Nutrition

Postinjury liver failure is generally not associated with pre-existing malnutrition. The systemic inflammatory responses after trauma result in hypermetabolism, thus leading to protein degradation and catabolism. In the liver, the hepatic synthesis of proteins switches from constitutive hepatic proteins to acute-phase proteins such as haptoglobin and c-reactive protein [61]. The hepatic acute-phase responses are directed at restoring homeostasis; nevertheless, an exacerbated process can lead to hypermetabolism and catabolism [62].

A significantly catabolic response secondary to liver failure requires nutritional support, not only to maintain nutrition balance, optimize metabolic arrangements, and meet energy requirements to minimize the effects of complications, but also to ameliorate human immune responses to infection [63].

Enteral feeding is preferable to parenteral feeding in patients with postinjury liver failure. Enteral feeding might be immunologically superior to parenteral feeding. Early enteral nutrition has been shown to be associated with a lower incidence of nosocomial infection [63]. Oral intake should be encouraged, although patients with MOF may be unconscious because of concomitant head injury or respiratory status or may be incapable of oral intake because of gastrointestinal injury and associated surgeries. Severe encephalopathy, in which the aspiration risk is high, or anorexia may prevent oral intake. Nasogastric or nasojejunal feeding is safe and readily performed in the ICU. In the case of delayed gastric emptying, postpylorus feeding might be required. Caution should be taken in enteral feeding in the setting of liver failure, which is often associated with intestinal failure with various clinical presentations including ileus, significant diarrhea leading to volume loss, malabsorption, and bacterial translocation [64]. Parenteral feeding may cause complications. Nosocomial infections are often associated with a central line, which is very frequently colonized. Multidrug resistant bacterial infections are more prevalent among patients with TPN, and such infections increase mortality [65]. Insulin has been demonstrated to decrease the incidence of MOF and mortality [66], since better glucose control provides anti-inflammatory effects. Several studies have suggested that insulin control of glucose serum levels attenuates the inflammatory response by decreasing proinflammatory cytokines and increasing anti-inflammatory cytokines [67].

13.4.9 Liver-Specific Treatment

Liver regeneration, including functional and structural recovery, is the ultimate goal of managing postinjury liver failure. The difficulty of understanding in liver failure has contributed to a lack of innovation in liver failure management. Blood

purification treatment, including hemodialysis and hemofiltration with or without plasma exchange, has been utilized to treat liver failure. Plasma exchange with hemodiafiltration appears to be capable of removing toxins leading to the improvement of coma in liver failure [68], although it failed to improve patients' survival [69]. Molecular adsorbent recirculating system (MARS) has been utilized as an advanced purification method for the last two decades, in which both water-soluble toxins and albumin-bound toxins can be eliminated through polysulfone membrane [70]. It was demonstrated that MARS improved short-term survival and has been utilized as a bridge to orthotopic liver transplantation [71]. The ultimate solution for postinjury liver failure is liver transplantation. Although the indications have not been described, several case reports of primary liver injury resulted in liver failure have been described in the literature. The indication highly depends on individual health systems and institutions [72].

13.5 Future Directions

Although postinjury liver failure is progressively becoming less common, it remains a highly lethal clinical condition. Currently, only supportive treatment measures are available. Artificial liver support systems can be utilized, nevertheless, all these systems are based on currently available hemodialysis techniques or plasmapheresis. New measures including hepatocyte or stem cell transplantation, tissue engineered-liver, and bioartificial liver system are currently under investigation. Bioartificial liver is an experimental device where hepatocytes are stored as a biological source of liver function and it aims to replace the whole liver function as a device [73]. Tissue-engineered liver has been explored to provide transplantable liver tissues or ultimately a whole liver, nevertheless, there are still many challenges remaining before this technology becomes applicable to clinical medicine [74]. The pathophysiology of liver failure, the hepatic inflammation cascade, complex immune system, and regeneration of the liver must be further explored. Organ bioengineering could be a vital area of interest in the future.

13.6 Summary

Liver failure in postinjury MOF is rare. Liver failure occurs in approximately one-fifth of trauma patients after the initial shock. Nevertheless, the majority of the patients only develop transit mild-moderate liver failure and reversible. Once persistent liver failure in the setting of late postinjury MOF is developed, its clinical management remains challenging despite advances in critical care management, and the associated mortality remains high. Preventive strategies including optimal resuscitation, early definitive surgery, if possible, and supportive ICU management are imperative. After liver failure is established, multiorgan supportive care is the best management. Further investigation of the complex immune mechanism and the pathophysiology of liver failure will be essential to improve the outcomes of postinjury liver failure.

References

1. Eiseman B, Beart R, Norton L. Multiple organ failure. Surg Gynecol Obstet. 1977;144(3):323–6.
2. Dewar DC, Tarrant SM, King KL, Balogh ZJ. Changes in the epidemiology and prediction of multiple-organ failure after injury. J Trauma Acute Care Surg. 2013;74(3):774–9.
3. Sauaia A, Moore EE, Johnson JL, Ciesla DJ, Biffl WL, Banerjee A. Validation of postinjury multiple organ failure scores. Shock. 2009;31(5):438–47.
4. Pak S, Kondo T, Nakano Y, Murata S, Fukunaga K, Oda T, et al. Platelet adhesion in the sinusoid caused hepatic injury by neutrophils after hepatic ischemia reperfusion. Platelets. 2010;21(4):282–8.
5. Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008;454(7203):428–35.
6. Heymann F, Peusquens J, Ludwig-Portugall I, Kohlhepp M, Ergen C, Niemietz P, et al. Liver inflammation abrogates immunological tolerance induced by Kupffer cells. Hepatology. 2015;62(1):279–91.
7. Gracia-Sancho J, Caparros E, Fernandez-Iglesias A, Frances R. Role of liver sinusoidal endothelial cells in liver diseases. Nat Rev Gastroenterol Hepatol. 2021;18(6):411–31.
8. Rodriguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome--a liver-induced lung vascular disorder. N Engl J Med. 2008;358(22):2378–87.
9. Varga ZV, Erdelyi K, Paloczi J, Cinar R, Zsengeller ZK, Jourdan T, et al. Disruption of renal arginine metabolism promotes kidney injury in hepatorenal syndrome in mice. Hepatology. 2018;68(4):1519–33.
10. Felipo V. Hepatic encephalopathy: effects of liver failure on brain function. Nat Rev Neurosci. 2013;14(12):851–8.
11. Moller S, Bernardi M. Interactions of the heart and the liver. Eur Heart J. 2013;34(36):2804–11.
12. Koch A, Streetz K, Tischendorf J, Trautwein C, Tacke F. Abnormal liver function tests in the intensive care unit. Med Klin Intensivmed Notfmed. 2013;108(7):599–608; quiz 9–10.
13. Jenniskens M, Langouche L, Vanwijngaerden YM, Mesotten D, Van den Berghe G. Cholestatic liver (dys)function during sepsis and other critical illnesses. Intensive Care Med. 2016;42(1):16–27.
14. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC. Postinjury multiple organ failure: a bimodal phenomenon. J Trauma. 1996;40(4):501–10; discussion 10–2.
15. Luedde T, Kaplowitz N, Schwabe RF. Cell death and cell death responses in liver disease: mechanisms and clinical relevance. Gastroenterology. 2014;147(4):765–83 e4.
16. Ciesla DJ, Moore EE, Johnson JL, Cothren CC, Banerjee A, Burch JM, et al. Decreased progression of postinjury lung dysfunction to the acute respiratory distress syndrome and multiple organ failure. Surgery. 2006;140(4):640–7; discussion 7–8.
17. Frohlich M, Lefering R, Probst C, Paffrath T, Schneider MM, Maegele M, et al. Epidemiology and risk factors of multiple-organ failure after multiple trauma: an analysis of 31,154 patients from the TraumaRegister DGU. J Trauma Acute Care Surg. 2014;76(4):921–7; discussion 7–8.
18. Moore EE, Moore FA, Harken AH, Johnson JL, Ciesla D, Banerjee A. The two-event construct of postinjury multiple organ failure. Shock. 2005;24(Suppl 1):71–4.
19. Dewar D, Moore FA, Moore EE, Balogh Z. Postinjury multiple organ failure. Injury. 2009;40(9):912–8.
20. Helling TS. The liver and hemorrhagic shock. J Am Coll Surg. 2005;201(5):774–83.
21. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet. 2014;383(9930):1749–61.
22. Henrion J, Schapira M, Luwaert R, Colin L, Delannoy A, Heller FR. Hypoxic hepatitis: clinical and hemodynamic study in 142 consecutive cases. Medicine (Baltimore). 2003;82(6):392–406.
23. Spapen H. Liver perfusion in sepsis, septic shock, and multiorgan failure. Anat Rec (Hoboken). 2008;291(6):714–20.
24. Jaeschke H. Molecular mechanisms of hepatic ischemia-reperfusion injury and preconditioning. Am J Physiol Gastrointest Liver Physiol. 2003;284(1):G15–26.
25. Jimenez-Castro MB, Cornide-Petronio ME, Gracia-Sancho J, Peralta C. Inflammasome-mediated inflammation in liver ischemia-reperfusion injury. Cells. 2019;8(10):1131.

26. Scatton O, Zalinski S, Jegou D, Compagnon P, Lesurtel M, Belghiti J, et al. Randomized clinical trial of ischaemic preconditioning in major liver resection with intermittent Pringle manoeuvre. Br J Surg. 2011;98(9):1236–43.
27. Ishizaki Y, Yoshimoto J, Miwa K, Sugo H, Kawasaki S. Safety of prolonged intermittent pringle maneuver during hepatic resection. Arch Surg. 2006;141(7):649–53; discussion 54.
28. Bajaj JS, O'Leary JG, Reddy KR, Wong F, Olson JC, Subramanian RM, et al. Second infections independently increase mortality in hospitalized patients with cirrhosis: the North American consortium for the study of end-stage liver disease (NACSELD) experience. Hepatology. 2012;56(6):2328–35.
29. Tacke F, Luedde T, Trautwein C. Inflammatory pathways in liver homeostasis and liver injury. Clin Rev Allergy Immunol. 2009;36(1):4–12.
30. Vollmar B, Glasz J, Leiderer R, Post S, Menger MD. Hepatic microcirculatory perfusion failure is a determinant of liver dysfunction in warm ischemia-reperfusion. Am J Pathol. 1994;145(6):1421–31.
31. Sindram D, Porte RJ, Hoffman MR, Bentley RC, Clavien PA. Platelets induce sinusoidal endothelial cell apoptosis upon reperfusion of the cold ischemic rat liver. Gastroenterology. 2000;118(1):183–91.
32. Strnad P, Tacke F, Koch A, Trautwein C. Liver - guardian, modifier and target of sepsis. Nat Rev Gastroenterol Hepatol. 2017;14(1):55–66.
33. Schnabl B, Brenner DA. Interactions between the intestinal microbiome and liver diseases. Gastroenterology. 2014;146(6):1513–24.
34. Singal AK, Salameh H, Kamath PS. Prevalence and in-hospital mortality trends of infections among patients with cirrhosis: a nationwide study of hospitalised patients in the United States. Aliment Pharmacol Ther. 2014;40(1):105–12.
35. Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol. 2014;60(6):1310–24.
36. Bleriot C, Dupuis T, Jouvion G, Eberl G, Disson O, Lecuit M. Liver-resident macrophage necroptosis orchestrates type 1 microbicidal inflammation and type-2-mediated tissue repair during bacterial infection. Immunity. 2015;42(1):145–58.
37. Yan J, Li S, Li S. The role of the liver in sepsis. Int Rev Immunol. 2014;33(6):498–510.
38. Jenne CN, Kubes P. Immune surveillance by the liver. Nat Immunol. 2013;14(10):996–1006.
39. Fuhrmann V, Kneidinger N, Herkner H, Heinz G, Nikfardjam M, Bojic A, et al. Hypoxic hepatitis: underlying conditions and risk factors for mortality in critically ill patients. Intensive Care Med. 2009;35(8):1397–405.
40. Brienza N, Dalfino L, Cinnella G, Diele C, Bruno F, Fiore T. Jaundice in critical illness: promoting factors of a concealed reality. Intensive Care Med. 2006;32(2):267–74.
41. Geier A, Fickert P, Trauner M. Mechanisms of disease: mechanisms and clinical implications of cholestasis in sepsis. Nat Clin Pract Gastroenterol Hepatol. 2006;3(10):574–85.
42. Kosters A, Karpen SJ. The role of inflammation in cholestasis: clinical and basic aspects. Semin Liver Dis. 2010;30(2):186–94.
43. Strazzabosco M, Fabris L, Spirli C. Pathophysiology of cholangiopathies. J Clin Gastroenterol. 2005;39(4 Suppl 2):S90–S102.
44. Jager B, Drolz A, Michl B, Schellongowski P, Bojic A, Nikfardjam M, et al. Jaundice increases the rate of complications and one-year mortality in patients with hypoxic hepatitis. Hepatology. 2012;56(6):2297–304.
45. Leonhardt S, Veltzke-Schlieker W, Adler A, Schott E, Hetzer R, Schaffartzik W, et al. Trigger mechanisms of secondary sclerosing cholangitis in critically ill patients. Crit Care. 2015;19:131.
46. Benninger J, Grobholz R, Oeztuerk Y, Antoni CH, Hahn EG, Singer MV, et al. Sclerosing cholangitis following severe trauma: description of a remarkable disease entity with emphasis on possible pathophysiologic mechanisms. World J Gastroenterol. 2005;11(27):4199–205.
47. Wohlauer MV, Sauaia A, Moore EE, Burlew CC, Banerjee A, Johnson J. Acute kidney injury and posttrauma multiple organ failure: the canary in the coal mine. J Trauma Acute Care Surg. 2012;72(2):373–8; discussion 9–80.

48. Thandassery RB, John A, Koshy RM, Al Kaabi S. Triad of post-ERCP pancreatitis, and gastric outlet, and biliary obstruction: are we dealing with intramural duodenal hematoma? Endoscopy. 2014;46(Suppl 1):UCTN:E443-4.
49. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. 2012;72(6):1491–501.
50. Benns M, Carr B, Kallan MJ, Sims CA. Benchmarking the incidence of organ failure after injury at trauma centers and nontrauma centers in the United States. J Trauma Acute Care Surg. 2013;75(3):426–31.
51. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301–8.
52. Offner PJ, Moore EE, Ciesla D. The adrenal response after severe trauma. Am J Surg. 2002;184(6):649–53; discussion 53–4.
53. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med. 2008;36(6):1937–49.
54. LeRoux PD, Elliott JP, Perkins JD, Winn HR. Intracranial pressure monitoring in fulminant hepatic failure and liver transplantation. Lancet. 1990;335(8700):1291.
55. Rangel-Castilla L, Gopinath S, Robertson CS. Management of intracranial hypertension. Neurologic Clinics. 2008;26(2):521–41, x. https://doi.org/10.1016/j.ncl.2008.02.003.
56. Kerbert AJ, Engelmann C, Jalan R. Neurocritical care management of hepatic encephalopathy and coma in liver failure. Semin Respir Crit Care Med. 2018;39(5):523–37.
57. Tormey WP. Central pontine myelinolysis and changes in serum sodium. Lancet. 1990;335(8698):1169.
58. Ong JP, Aggarwal A, Krieger D, Easley KA, Karafa MT, Van Lente F, et al. Correlation between ammonia levels and the severity of hepatic encephalopathy. Am J Med. 2003;114(3):188–93.
59. Biggins SW, Angeli P, Garcia-Tsao G, Gines P, Ling S, Nadim MK, et al. Diagnosis, evaluation, and management of ascites and hepatorenal syndrome. Hepatology. 2021;74:1014.
60. Slack AJ, Auzinger G, Willars C, Dew T, Musto R, Corsilli D, et al. Ammonia clearance with haemofiltration in adults with liver disease. Liver Int. 2014;34(1):42–8.
61. Heymann F, Tacke F. Immunology in the liver--from homeostasis to disease. Nat Rev Gastroenterol Hepatol. 2016;13(2):88–110.
62. O'Brien A, Williams R. Nutrition in end-stage liver disease: principles and practice. Gastroenterology. 2008;134(6):1729–40.
63. Kudsk KA. Beneficial effect of enteral feeding. Gastrointest Endosc Clin N Am. 2007;17(4):647–62.
64. Nicoletti A, Ponziani FR, Biolato M, Valenza V, Marrone G, Sganga G, et al. Intestinal permeability in the pathogenesis of liver damage: from non-alcoholic fatty liver disease to liver transplantation. World J Gastroenterol. 2019;25(33):4814–34.
65. Choudhuri AH, Khurana P, Biswas PS, Uppal R. Epidemiology and risk factors for multidrug-resistant bacteria in critically ill patients with liver disease. Saudi J Anaesth. 2018;12(3):389–94.
66. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359–67.
67. van Niekerk G, Christowitz C, Conradie D, Engelbrecht AM. Insulin as an immunomodulatory hormone. Cytokine Growth Factor Rev. 2020;52:34–44.
68. Oda S, Hirasawa H, Shiga H, Nakanishi K, Matsuda K, Nakamura M. Continuous hemofiltration/hemodiafiltration in critical care. Ther Apher. 2002;6(3):193–8.
69. Garcia Martinez JJ, Bendjelid K. Artificial liver support systems: what is new over the last decade? Ann Intensive Care. 2018;8(1):109.
70. Stange J, Hassanein TI, Mehta R, Mitzner SR, Bartlett RH. The molecular adsorbents recycling system as a liver support system based on albumin dialysis: a summary of preclinical

investigations, prospective, randomized, controlled clinical trial, and clinical experience from 19 centers. Artif Organs. 2002;26(2):103–10.
71. Hanish SI, Stein DM, Scalea JR, Essien EO, Thurman P, Hutson WR, et al. Molecular adsorbent recirculating system effectively replaces hepatic function in severe acute liver failure. Ann Surg. 2017;266(4):677–84.
72. Krawczyk M, Grat M, Adam R, Polak WG, Klempnauer J, Pinna A, et al. Liver transplantation for hepatic trauma: a study from the european liver transplant registry. Transplantation. 2016;100(11):2372–81.
73. He YT, Qi YN, Zhang BQ, Li JB, Bao J. Bioartificial liver support systems for acute liver failure: a systematic review and meta-analysis of the clinical and preclinical literature. World J Gastroenterol. 2019;25(27):3634–48.
74. Hou YT, Hsu CC. Development of a 3D porous chitosan/gelatin liver scaffold for a bioartificial liver device. J Biosci Bioeng. 2020;129(6):741–8.

Gastrointestinal Failure, Clinical Presentations, and Treatment

14

Annika Reintam Blaser, Joel Starkopf, and Stephan M. Jakob

14.1 Definition of Gastrointestinal Failure

Definition of GI failure depends on the focus on specific functions of gastrointestinal organs. Besides absorption, digestion, and excretion these functions include endocrine and immune functions among others. Working Group on Abdominal Problems of European Society of Intensive Care Medicine (ESICM) has proposed a term Acute Gastrointestinal Injury (AGI) to describe GI dysfunction as a part of multiple organ dysfunction syndrome (MODS) [1]. AGI is descriptively divided into four levels of increasing grade (see Table 14.1 with clinical examples). In the context of post-injury GI dysfunction, direct lesions, including those caused by surgery, and side effects of treatment are of special interest. The examples include bowel edema due to massive fluid resuscitation, splanchnic hypoperfusion due to high-dose vasoconstrictor administration—mostly in the context of insufficient fluid replacement/ongoing hemorrhage—and bowel paralysis resulting from opioids (see Sects. 14.3.3 and 14.5.1).

A. Reintam Blaser (✉)
Department of Anaesthesiology and Intensive Care, University of Tartu, Tartu, Estonia

Department of Intensive Care Medicine, Lucerne Cantonal Hospital, Lucerne, Switzerland
e-mail: annika.reintam.blaser@ut.ee

J. Starkopf
Department of Anaesthesiology and Intensive Care, University of Tartu, Tartu, Estonia

Department of Anaesthesiology and Intensive Care, Tartu University Hospital, Tartu, Estonia
e-mail: joel.starkopf@kliinikum.ee

S. M. Jakob
Department of Intensive Care Medicine, Inselspital, University of Bern, Bern, Switzerland
e-mail: stephan.jakob@insel.ch

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_14

Table 14.1 Acute gastrointestinal injury (AGI) and grades of severity (modified after [2])

Grade	Description	Definition	Rationale	Examples
AGI Grade I	Risk of developing GI dysfunction or failure	The function of the GI tract is partially impaired, expressed as GI symptoms related to a known cause and perceived as transient	Occurrence of GI symptoms after an insult, which expectedly has temporary and self-limiting nature	Postoperative nausea and vomiting, absent bowel sounds after abdominal surgery
AGI Grade II	GI dysfunction	The GI tract is not able to perform digestion and absorption adequately to satisfy the nutrient and fluid requirements of the body. There are no obvious changes in general condition of the patient related to GI problems	Acute GI symptoms requiring therapeutic interventions for achievement of nutrient and fluid requirements. This condition occurs without previous GI interventions or is more severe than might be expected in relation to the course of preceding abdominal procedures	Gastroparesis with high GRVs, paralysis of the lower GI tract, diarrhea, IAP 12–15 mmHg, visible blood in gastric content or stool
AGI grade III	GI failure	Loss of GI function, where restoration of GI function is not achieved despite interventions and the general condition is not improving	Sustained intolerance to EN without improvement after treatment (e.g. erythromycin, post-pyloric tube placement), along with persistence or worsening of MODS	High GRVs and persisting GI paralysis despite treatment, occurrence or worsening of bowel dilatation, progression of IAH to grade II (IAP 15–20 mmHg)
AGI grade IV	GI failure with severe impact on distant organ function	AGI has progressed to become directly and immediately life-threatening, with worsening of MODS and shock	Situation when AGI has led to an acute critical deterioration of the general condition of the patient with distant organ dysfunction(s)	Bowel ischemia with necrosis, GI bleeding leading to hemorrhagic shock, Ogilvie's syndrome, abdominal compartment syndrome

EN enteral nutrition, *GI* gastrointestinal, *GRV* gastric residual volume, *IAH* intra-abdominal hypertension, *IAP* intra-abdominal pressure, *MODS* multiple organ dysfunction syndrome

14.2 Pathophysiology and Impact on Outcome

14.2.1 Primary and Secondary GI Injury

Primary GI injury comprises mainly penetrating and non-penetrating injuries of the GI tract including pancreas, bile duct, and mesenteric vessels. Pathophysiology depends on the mechanism and magnitude of trauma and concomitant involvement of other body regions such as thorax and retroperitoneum, which may increase intra-abdominal pressure (IAP) and thereby decrease venous return [3]. Furthermore,

damage control resuscitation may also increase IAP and cause or aggravate AGI. Even though an open abdomen approach is effective in reducing IAP, it can also result in major complications. Respective management guidelines have recently been published by the World Society of Emergency Surgery [4].

In GI tract injuries, large amounts of GI fluids may be lost. If the colon is involved, abdominal infection, often with sepsis, will occur. Pancreatic trauma is relatively rare but associated with significant mortality rates, probably related to associate (vascular) injuries [5]. In animal models, pancreatic injury is associated with cytokine release and aggravates secondary AGI and MODS [6].

Secondary GI injury after trauma or hemorrhage outside of GI system results from hypovolemia due to fluid/blood loss and bowel ischemia in case of severe hemorrhage [7], especially if combined with vasoconstrictors. Hypoxemia, vasoconstriction, and bacterial translocation after brain trauma [8] are additional triggers without major blood loss. The so-called danger signals (danger-associated molecular patterns, DAMP), substances released from "stressed" cells, are increasingly recognized as part of the post-traumatic immune response [9]. In general, such molecules exhibit intracellular physiological roles but acquire new functions when released into the extracellular space. They can trigger remote organ dysfunction several days after trauma. Further, and more immediately, support of other than abdominal organs can also bear the risk of impairing functions of gastrointestinal organs. Examples are dialysis causing hypovolemia and high airway pressure increasing IAP and impeding venous return and cardiac output, which may further jeopardize bowel perfusion.

Pathophysiological mechanisms of primary and secondary AGI after trauma are presented in Fig. 14.1.

14.2.2 Impact on ICU Outcome

In MODS in trauma patients, individual failing organs contribute to mortality [10]. GI failure defined as presence of acalculous cholecystitis, stress ulcer, or GI bleeding was initially included in the first multiple organ failure score (MOF score) [11], but excluded later due to rare incidence and lacking association with mortality [12]. Currently, GI dysfunction/injury is not directly included in any organ dysfunction score [13] mainly due to the difficulty to score GI (dys)function. Conversely, several concomitant signs and symptoms of GI injury such as high gastric residual volume, absent bowel sounds, vomiting or regurgitation, diarrhea, bowel distension, and gastrointestinal bleeding have been independently associated with unfavorable outcomes, including mortality [14, 15]. The most important functions of the GI tract for determination of outcome besides direct consequences of trauma are probably its barrier and immune functions. However, there is merely indirect evidence and data from animal experiments to support this assumption. Briefly, it has been shown that GI hypo- and re-perfusion may damage the mucosal barrier and lead to inflammatory and immunologic reactions as a result of translocation of biologically active compounds into blood and mesenteric lymphatics [16, 17]. These reactions may trigger remote organ failure, especially of the lung.

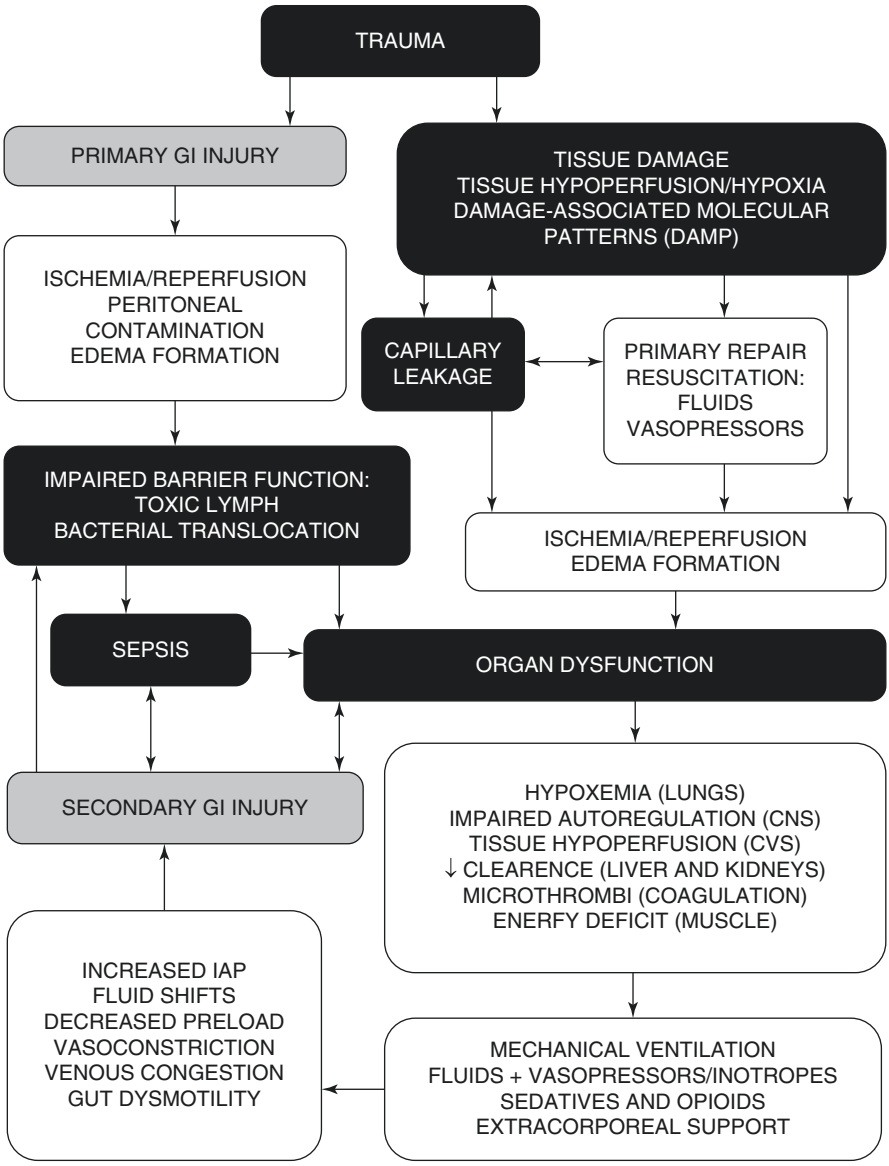


Fig. 14.1 Main pathophysiological mechanisms of primary and secondary GI injury after severe trauma (modified after [2]). *GI* gastrointestinal, *CNS* central nervous system, *CVS* cardiovascular system, *IAP* intra-abdominal pressure

14.3 Clinical Presentation

14.3.1 Abdominal Signs in Early Post-injury/Postoperative Period

GI dysfunction/AGI cannot usually be diagnosed very early in post-injury/postoperative period. Naturally, direct traumatic lesions to abdomen suggest the risk or presence of AGI. Therefore, intraoperative observations such as edematous, discolored, or distended bowel are not only important for choosing the surgical strategy (formation of anastomosis vs. stoma, planning of "second look," etc.), but also for planning the postoperative enteral nutrition (EN).

After severe trauma the patient is often sedated and mechanically ventilated. Large amounts of fluids have often been administered and the need for fluids may continue. Accordingly, signs and symptoms commonly used for recognition of AGI (addressed in Sect. 14.4.1) may not be possible to evaluate and correctly interpret. However, repeated and standardized evaluation of GI symptoms needs to start immediately after ICU admission. This will help to understand the dynamics of MODS and to identify the need of (re)operation.

Current approach to AGI does not address specific situations after trauma surgery. In damage control surgery, temporary closure of the abdomen is usually performed, and reoperation is scheduled. In such cases attention should be paid to the aspect of abdominal drainage (blood or feces) and blood lactate levels to detect possible bleeding, perforation, or bowel ischemia (see also Sect. 14.4.4).

Abdominal injury may necessitate extensive bowel resection resulting in short bowel syndrome. This does not necessarily lead to immediate unfavorable outcome such as death or MODS, but rather to chronic intestinal failure [18].

Taken together, based on initial presentation it is not possible to predict whether AGI will become relevant in promoting organ failure and thereby influencing short-time outcome.

14.3.1.1 Abdominal Pain

Abdominal pain is important diagnostic sign in emergency medicine setting. In severely injured and/or post-laparotomy ICU patients, assessment of pain is often limited. If the patient is awake, systematic and regular assessment of pain by standardized procedure and documentation of Numerical Rating Scale (NRS) is recommended [19].

14.3.1.2 Distended Abdomen

Abdominal distension is a subjective sign, difficult to assess and interpret. Measurements of IAP are strongly advocated to overcome this subjectivity [20] (see Sect. 14.3.2). This applies not only for abdominal trauma, but for severe polytrauma patients in general. Increasing abdominal distension/IAP may refer to intra-abdominal/retroperitoneal bleeding, perforation, or bowel distension possibly associated with bowel ischemia. Triggers for immediate multidisciplinary re-evaluation (surgeon, intensivist, anesthetist) as well as possible signs suggesting the need for reoperation need to be discussed and agreed a priori.

Presence/absence of relevant bleeding needs to be assessed repeatedly using abdominal ultrasound additionally to frequently scheduled laboratory assessment (hemoglobin level and lactate). Possible pitfalls (hemoglobin depending on hemodilution, hyperlactatemia on global oxygen delivery, and ultrasound finding being inconclusive in case of intra-abdominal/intra-luminal gas) need to be anticipated and a plan for further diagnostics vs. immediate intervention established.

14.3.2 Intra-Abdominal Hypertension

Even though IAP does not reflect the GI function directly, it is the most valuable parameter in the acute setting to monitor processes in abdominal compartment. Intra-abdominal hypertension (IAH) rarely seems to occur without concomitant GI symptoms [21], and several abdominal signs and symptoms were identified as being independently associated with development of IAH during ICU stay [22]. However, relationship between GI injury and IAP may be bi-directional. Applying measurements of IAP to patients presenting with risk factors of IAH and monitoring dynamics of IAP may not only detect IAH jeopardizing organ function, but also assist in decisions regarding nutrition and early recognition of threatening.

14.3.3 GI Dysmotility

Motility is not a function of GI system, but is necessary prerequisite to perform digestive function [23]. GI motility is a complex process, controlled by several neurohumoral mechanisms [24], and is difficult to monitor [25]. Importantly, motility is not only propulsion of bowel contents. Churning, mixing, and creating a reservoir are equally important elements of this process. There are different concepts regarding motility changes after injury or surgery [26]. Some evidence suggests that small bowel is best preserved and gastric motility most impaired [27]. The prevalent motility pattern in colon is retrograde, to allow sufficient time for absorption and avoid overfilling of rectum (“rectosigmoidal brake”). Evaluating the bowel motility based on frequency of stool passage therefore may not be correct. Still, bowel paralysis after injury or surgery is concerning issue, as it may lead to severe bowel distension, ischemia, or perforation, thought to lead to bacterial translocation and thereby (re)-commencing multiple organ dysfunction [28].

Conversely, too fast passage expressed as diarrhea is usually associated with malabsorption. It has been shown that with a stool weight >350 g/day around 1/3 of enterally administered calories are not taken up by the bowel [29].

Options to monitor motility are very limited. Gastric residual volume (GRV) may help to roughly estimate gastric emptying. Importantly, one large study suggesting that measurement of gastric residuals is obsolete was performed in medical patients with already installed full EN [30]. Therefore, gastric aspirate volumes (without EN) or GRV (with EN) still should be considered useful in patients after abdominal surgery and during starting phase of EN [31]. In the future, ultrasound

may offer an alternative to GRV and possibly also assist in evaluation of bowel motility beyond stomach, but respective protocols should be developed first and specific training is needed to reduce inter-observer variability [32].

Importantly, absence of peristalsis in auscultation does not mean complete quiescence of the bowel, whereas presence of peristalsis on auscultation does not indicate normal motility pattern. Even though complete absence of bowel sounds is abnormal and occurs commonly in most severely ill patients [15], any management decisions (incl. on starting or withholding enteral nutrition) should not be based on the presence or absence of bowel sounds [33].

14.3.4 Feeding Intolerance

Even though feeding intolerance is an important and well-accepted sign in management of critically ill patients, it is not uniformly defined [34]. Gastric residual volumes with different cut-offs are most often used to define feeding intolerance, detected in one-fourth to one-third of ICU patients [35]. Feeding challenge is needed to diagnose feeding intolerance; therefore, decision to test the tolerance needs to be taken first [36]. Reasons to delay EN (not to test feeding tolerance) in critically ill patients are uncontrolled shock, uncontrolled hypoxemia and acidosis, uncontrolled upper GI bleeding, gastric aspirate volume >500 mL/6 h, bowel ischemia, bowel obstruction or discontinuity, abdominal compartment syndrome, and high-output fistula without distal feeding access [33].

14.4 Monitoring of GI Function

Bedside assessment of GI function consists of thorough clinical examination together with measurements of GRV and complementary monitoring of IAP. Together with blood acid-base status and lactate measurements this should aim for timely recognition of abdominal problems requiring radiological imaging and/or intervention and take decisions regarding of EN.

14.4.1 GI Symptoms

GI symptoms such as vomiting/regurgitation, large GRVs, bowel paralysis, bowel dilatation and distension, melena, and diarrhea are frequent in intensive care patients, including after multiple trauma [15, 37].

There is limited data on individual symptoms specifically in post-injury patients; therefore, we address GI symptoms in general ICU population.

GRV can be measured passively by gravity drainage or actively via aspiration, whereas neither technique is validated nor standardized. Gastric ultrasound could be an alternative to estimate gastric filling, but is observer-dependent and may be unreliable [32]. GRV thresholds vary largely, but usually GRV is considered being

increased when exceeding 200 mL in a single measurement, or 1000 mL during 24 h [1]. However, GRV of 200 mL should not be used as a cut-off to neither delay nor discontinue EN, whereas GRV above 500 mL/6 h should be considered a cut-off to discontinue EN and should trigger search for undiagnosed abdominal problems and if excluded, consideration of prokinetic therapy.

Paralysis of lower GI tract (paralytic ileus) is defined as absence of stool for 3 or more consecutive days without mechanical obstruction, whereas bowel sounds may be absent or present [1]. Bowel paralysis defined as described occurs in majority of the patients staying in the ICU for 3 days or longer [38] and may be just observed unless associated with bowel dilatation or distension and increase in IAP. At the same time increased attention and daily re-evaluation is crucial, because lower GI paralysis may be a sign of new/unresolved acute pathology in the abdomen (e.g. peritonitis, ischemia).

Bowel dilatation is radiological diagnosis, not necessarily expressed in any clinical symptoms. Bowel distension refers to expansion through increased intra-luminal pressure, commonly manifesting in symptoms such as bloating or pain. Bowel distension may lead to vasovagal reactions, bacterial translocation, and subsequent systemic inflammation [39] and eventually to bowel perforation. Next to bowel dysmotility, excessive gas production by gut microflora has a role in pathogenesis of bowel distension without mechanical obstruction.

Melena is defined as darkening of the feces by blood pigments. Of note, clinically relevant bleeding may initially be masked by concomitant bowel paralysis. Melena may also indicate presence of mesenteric ischemia and always should trigger assessment of other GI symptoms, laboratory values, and consideration of imaging.

Diarrhea is defined as simultaneous presence of three or more stools per day, stool weight 200 g/day or higher, and consistency of stools categorized as 5–7 on the Bristol Stool Chart [40]. Diarrhea occurs in 1/5 of patients in the ICU [40], increasing to 2/3 in patients staying for 5 days and receiving EN for >3 days [41]. Diarrhea is often associated with prokinetic and laxative therapy, but may also be a sign of intestinal ischemia. Importantly, diarrhea is associated with malabsorption [29].

14.4.2 Scoring Systems

Different scoring systems have been proposed in the past for description of GI failure [2]. The approach of researchers and experts is very different, depending to some extent on the primary area of interest. Terminology, definition, and descriptive grading of AGI (see Sect. 14.1 and Table 14.1) were proposed to overcome the confusion in terminology, recommending a standardized approach to GI dysfunction in critically ill patients.

14.4.3 Imaging

Radiologic imaging is an integral part in initial phase of trauma management. Vast majority of severe trauma patients receive computed tomography (CT) or ultrasound assessment to identify critical lesions requiring surgical care.

In postoperative/post-injury period the radiologic imaging remains important in identification of abdominal complications as underlying reasons of AGI. The indication for imaging has to be substantiated by the clear hypothesis driven from detailed clinical assessment (see above). There are no clear recommendations when which imaging technique should be performed. During the early phase after trauma, criteria for repeated imaging based on initial injury and surgery should be agreed in advance. The cumulative exposure to radiation has to be kept in mind, especially in children and young adults.

Ultrasound is a readily available first line investigation able to give a quick bedside image, especially in suspicion of intra-abdominal fluid collections. Ultrasound is also useful for assessment of gall bladder and bile ducts for guiding of percutaneous drainages. In combination with Doppler imaging it allows assessment of blood flow, being often used for qualitative single time-point evaluation of portal, hepatic, and renal blood flow after respective injury/surgery. The limitations of ultrasound are operator-dependency and disturbances caused by postoperative presence of intra-abdominal air or CO_2.

Plain X-ray of the abdomen is of limited utility. It may be indicated for follow up of enteral tube positioning and for assessment of bowel diameter in suspicion of bowel distension/acute colonic pseudo-obstruction (Ogilvie's syndrome). Diagnostic thresholds for bowel dilatation are 3 cm for small bowel, 6 cm for colon, and 9 cm for caecum, respectively [42, 43]. Dynamic series of plain X-ray with contrast media may give valuable information on bowel length and GI motility. The oro-cecal transit time, measured by different methods, is highly variable, but the approximate value in healthy individuals is 2–2.5 h [44].

CT imaging remains the method of choice in the diagnostic workout for most of the cases. Enteral combined with intravenous contrast is commonly recommended for assessment of the continuity of GI tract, possible continuing bleeding, the blood supply to abdominal organs, and intra- or extraperitoneal fluid collections (hematomas, abscesses). The contrast enhancement in arterial and venous phases (the biphasic protocol) is recommended if mesenteric ischemia is suspected. The arterial phase (with 1 mm slice thickness) enables accurate detection of vascular pathology and detailed reconstructions of the main mesenteric arteries and even collaterals, while the venous phase is required for the assessment of bowel wall and solid organ perfusion and integrity.

Magnetic resonance imaging (MRI) can provide superior imaging in certain clinical contexts (e.g. assessment of biliary anatomy/bile duct stones), but requires longer image acquisition times and necessitates specific metal free equipment which limits its use in the critically ill.

Digital subtraction angiography is indicated for therapeutic interventions rather than just plain diagnostics. Possible clinical scenarios include but are not limited to ongoing hemorrhage, e.g. in pelvic fracture or spleen rupture.

14.4.4 Biomarkers

Specific serological biomarkers for enterocyte function and mesenteric ischemia have been actively investigated during the last decade, but no new biomarker has yet made its way into clinical practice [45]. Nonspecific markers such as blood lactate and common inflammatory markers (C-reactive protein, procalcitonin, and leucocyte count) are still the only tools next to clinical assessment to suspect abdominal complications in the ICU. Increased blood lactate is suggested to be indicative of transmural bowel ischemia [18], whereas an early marker would be needed to avoid bowel necrosis. Moreover, in patients after severe trauma all abovementioned nonspecific markers are even less reliable due to extensive tissue trauma and systemic inflammatory response reaction.

Novel possible biomarkers for mesenteric ischemia are summarized in a recent systematic review [46]. Importantly, different assays and kits with different reference values are used and available studies are difficult to compare.

Citrulline is an interesting biomarker reflecting enterocyte mass in chronic GI diseases [47, 48]. Whether this biomarker is able to assist in diagnosis of GI function (reflecting reduced function of enterocytes) in critical illness is currently unclear. A major issue is that citrulline is metabolized in kidneys, and increased levels (possibly masking low levels due to decreased synthesis in enterocytes) are expected in acute kidney injury, common in critical illness, and even more so in severe trauma.

14.4.5 Other

Gastrointestinal tonometry may be used to assess splanchnic perfusion/tissue hypoxia as the gastric pCO_2 gap has been shown to correlate with outcome in ventilated ICU patients [49]. Other methods to assess splanchnic perfusion include refractance spectrophotometry, infrared spectroscopy, laser Doppler flowmetry, indocyanine green plasma disappearance rate, and videomicroscopic imaging techniques [50].

Monitoring of microbiome is currently thought to be promising in many medical subspecialties. Existing preliminary evidence in critically ill and trauma patients shows dysbiosis with reduced bacterial diversity, association with disease severity and possibly outcome, but large interpersonal variations complicate the interpretation [51–53].

Recently, high-resolution impedance manometry for monitoring of GI dysmotility has been tested in a small study in mechanically ventilated patients in the ICU, revealing grossly abnormal motility of the upper GI tract in all studied (n = 16) patients [54].

14.5 ICU Management of GI Injury

14.5.1 General Principles

As for any organ function, sufficient global blood flow and oxygen delivery need to be first achieved. However, hemodynamic coherence between macro- and microcirculation (situation where systemic resuscitation is effective in correcting organ perfusion and oxygenation) is often disturbed in critical illness [55]. Monitoring of microcirculation would be especially desirable for GI system, but is currently not available at bedside [56].

The following treatments applied in the ICU may influence GI function: (1) fluid, glucose and electrolyte management; (2) vasoconstrictors; (3) sedation and analgesia.

Excessive fluid resuscitation leads to bowel edema and causes GI dysfunction. However, insufficient fluid resuscitation leads to prolonged hypovolemia and vasoconstriction impairing organ function. More renal complications were observed with a restrictive approach of perioperative fluid management in abdominal surgery in a recent large randomized controlled trial, whereas no difference in GI dysfunction [57]. Euvolemia should be aimed to minimize further damage, but tools to steer fluid management to maintain euvolemia in critical illness with excessive stress response and capillary leak are lacking.

Hyperglycemia has been shown to slow gastric emptying [58], whereas hypokalemia and hypomagnesemia may impair bowel motility [59, 60]. Normal levels of plasma electrolyte and glucose levels should be aimed, whereas there is no data to support specific thresholds to improve GI motility.

Sufficient analgesia is crucial and often sedation is necessary in severely injured patients, whereas opioid analgetics and different types of sedatives are known to inhibit GI motility [60]. Multimodal analgesic regimens and morphine restriction have been demonstrated to improve recovery of GI function after elective surgery [61]. However, this may also be related to the positive effect of early mobilization known to improve GI motility, but not usually applicable to severe trauma patients.

IAH impairs splanchnic blood flow and may exacerbate bowel edema, thereby impairing GI function. However, there is no data that any intervention lowering IAP is able to improve GI function [62].

It needs to be underlined that patients with severe trauma almost inevitably develop substantial capillary leak leading to tissue (including bowel) edema and potentially IAH. In most of the cases, these problems are likely to resolve with redistribution of fluids after resolution of inflammatory state. However, monitoring that allows timely recognition if, e.g. IAH itself becomes threatening is crucial. Recognition of bowel edema or distension will call to caution regarding increase in the amount of enteral nutrition.

14.5.2 Nutrition

Early EN has been shown to be beneficial in critically ill patients in several meta-analyses [33, 63], including a specific analysis in trauma patients [64]. However, most

of the studies on early EN on trauma patients are old and present low data quality [64]. Moreover, many strategies in management of critical illness in these older studies (including surgical jejunostomy for EN) are not commonly used any more.

However, in the absence of contraindications to EN (see Sect. 14.3.4) early EN is considered beneficial [33]. Importantly, "early" is defined as within 48 h and early EN should always be started slowly and increased gradually under monitoring of GI symptoms (tolerance of enteral feeding) and IAP.

Parenteral nutrition (PN) has until recently been thought to be harmful but this belief has been challenged by recent studies [65, 66]. Additionally to results from several studies [65–68], recognition of concepts of endogenous energy production and suppression of autophagy by nutrients [69, 70] has led to understanding that achieving 100% of energy expenditure via any route early in the acute phase of severe illness is harmful. Additionally, early full EN in shock patients has recently been shown to result in more GI cases with intestinal ischemia as well as Ogilvie's syndrome [66].

Presence of bowel edema and distension are signs that call to caution regarding EN; however, they are not easy to assess at bedside. The concept of EN helping to maintain mucosal integrity is still valid. Therefore, hypothetically, feeding bowel mucosa and microbiome with a low amount of EN and adding supplemental PN after the early acute phase [71] could be an option in injured bowel. However, respective evidence is scarce, showing that trophic EN is not inferior to full EN [72, 73] and adding supplemental PN after the early acute phase may be slightly beneficial [74].

14.5.3 Specific Aspects of Primary GI Injury

Specific aspects in the management of primary GI injury are related to primary lesions in GI tract. Presence of bowel anastomosis should not be a reason to delay EN, whereas edematous and distended bowel may necessitate very careful progression of EN. Mesenteric vascular injuries may require anticoagulants or antiplatelet drugs, whereas pro-contra arguments in the early phase after severe trauma need to be carefully weighed.

There is lacking evidence but physiological rationale to delay EN in pancreatic injury in fear of promoted development of pancreatic fistula due to stimulation of secretion with EN.

14.5.4 Specific Aspects of Secondary GI Injury

Secondary GI injury after severe trauma is always a part of MODS. The concept of AGI includes assessment of general condition of patient (dynamics of other organ dysfunctions together with GI dysfunction) (Table 14.1 and Fig. 14.2). Such approach may help to better follow the course of illness at bedside and identify the role of GI dysfunction in MODS.

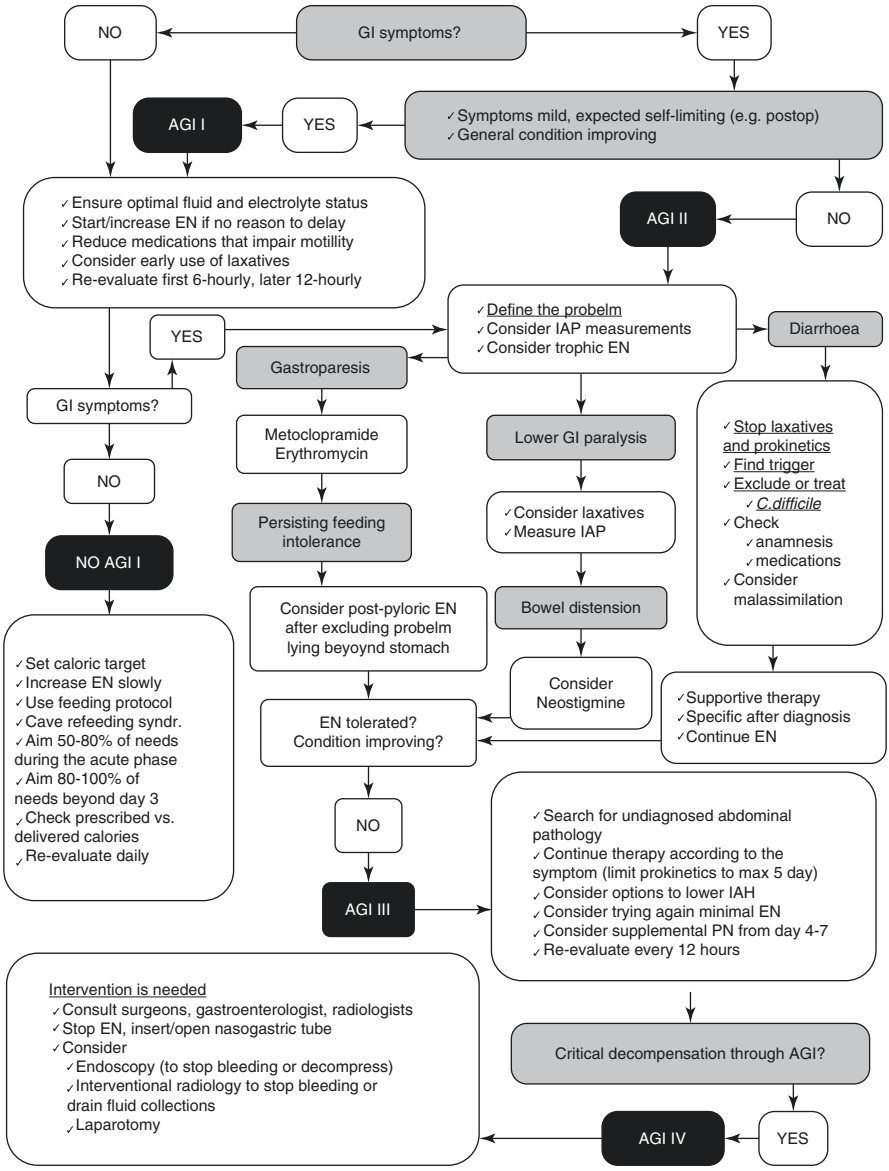


Fig. 14.2 Assessment and management of different grades of acute gastrointestinal injury (AGI) (modified after [2]). *EN* enteral nutrition, *IAH* intra-abdominal hypertension, *IAP* intra-abdominal pressure, *PN* parenteral nutrition

14.6 Unsolved Issues/Future Directions

Developments in monitoring of GI function allowing inclusion of GI dysfunction in scoring systems for MODS are most warranted. A comprehensive spectrum of future studies on GI function in critically ill, including monitoring, management, and pathophysiological mechanisms, has been recently outlined through multiple systematic reviews [75].

Substantial changes in intestinal microflora related to severe injury need to be further explored and diagnostic and therapeutic targets linked to microbiome investigated [51].

Future studies with immediate practical value, especially important in post-injury patients, should study:

- options for dynamic monitoring of bowel motility, bowel diameter, and edema;
- strategies to best steer fluid resuscitation to achieve optimal perfusion without excessive fluid overload;
- nutrition strategies in patients with AGI (both primary and secondary).

14.7 Summary

Clinical signs and symptoms associated with GI tract dysfunction are common in ICU patients, including after multiple trauma, and are related to impaired outcome. Clinical evaluation, complemented with assessment of gastric filling and intra-abdominal pressure, remains the main bedside tool to assess GI function and detect possible problems requiring investigations or interventions. Acute gastrointestinal injury (AGI) describes GI dysfunction as a part of MODS. AGI includes descriptive grading for bedside management, while search for objective and reproducible scoring system is continuing.

References

1. Reintam Blaser A, Malbrain ML, Starkopf J, Fruhwald S, Jakob SM, De Waele J, Braun JP, Poeze M, Spies C. Gastrointestinal function in intensive care patients: terminology, definitions and management. Recommendations of the ESICM Working Group on Abdominal Problems. Intensive Care Med. 2012;38(3):384–94.
2. Reintam Blaser A, Jakob SM, Starkopf J. Gastrointestinal failure in the ICU. Curr Opin Crit Care. 2016;22(2):128–41. https://doi.org/10.1097/MCC.0000000000000286.
3. Dagar G, Taneja A, Nanchal RS. Abdominal circulatory interactions. Crit Care Clin. 2016;32(2):265–77.
4. Coccolini F, Roberts D, Ansaloni L, Ivatury R, Gamberini E, Kluger Y, Moore EE, Coimbra R, Kirkpatrick AW, Pereira BM, Montori G, Ceresoli M, Abu-Zidan FM, Sartelli M, Velmahos G, Fraga GP, Leppaniemi A, Tolonen M, Galante J, Razek T, Maier R, Bala M, Sakakushev B, Khokha V, Malbrain M, Agnoletti V, Peitzman A, Demetrashvili Z, Sugrue M, Di Saverio S, Martzi I, Soreide K, Biffl W, Ferrada P, Parry N, Montravers P, Melotti RM, Salvetti F, Valetti TM, Scalea T, Chiara O, Cimbanassi S, Kashuk JL, Larrea M, Hernandez JAM, Lin HF,

Chirica M, Arvieux C, Bing C, Horer T, De Simone B, Masiakos P, Reva V, DeAngelis N, Kike K, Balogh ZJ, Fugazzola P, Tomasoni M, Latifi R, Naidoo N, Weber D, Handolin L, Inaba K, Hecker A, Kuo-Ching Y, Ordoñez CA, Rizoli S, Gomes CA, De Moya M, Wani I, Mefire AC, Boffard K, Napolitano L, Catena F. The open abdomen in trauma and non-trauma patients: WSES guidelines. World J Emerg Surg. 2018 Feb;2(13):7.

5. Mohseni S, Holzmacher J, Sjolin G, Ahl R, Sarani B. Outcomes after resection versus non-resection management of penetrating grade III and IV pancreatic injury: a trauma quality improvement (TQIP) databank analysis. Injury. 2018;49(1):27–32.
6. Gao H, Song Q, Lv F, Shi B, Wang P, Wang Y, Zhang Y, Yang L, Luo Y, Mei X, Tang J. Establishment and evaluation of a Beagle model of grade III pancreatic trauma. Exp Ther Med. 2018;16(4):3452–8. https://doi.org/10.3892/etm.2018.6656.
7. Reilly PM, Wilkins KB, Fuh KC, Haglund U, Bulkley GB. The mesenteric hemodynamic response to circulatory shock: an overview. Shock. 2001;15(5):329–43. https://doi.org/10.1097/00024382-200115050-00001.
8. Patterson TT, Nicholson S, Wallace D, Hawryluk GWJ, Grandhi R. Complex feed-forward and feed-back mechanisms underlie the relationship between traumatic brain injury and the gut-microbiota-brain axis. Shock. 2018;52:318.
9. Bortolotti P, Faure E, Kipnis E. Inflammasomes in tissue damages and immune disorders after trauma. Front Immunol. 2018;16(9):1900.
10. Antonelli M, Moreno R, Vincent JL, Sprung CL, Mendoça A, Passariello M, Riccioni L, Osborn J. Application of SOFA score to trauma patients. Sequential organ failure assessment. Intensive Care Med. 1999;25(4):389–94.
11. Goris RJA, Boekhorst TPA, Nuytinck JKS, Gimbrere JS. Multiple-organ failure. Arch Surg. 1985;120:1109–15.
12. Lefering R, Goris RJA, van Nieuwenhoven EJ, Neugebauer E. Revision of the multiple organ failure score. Langenbeck's Arch Surg. 2002;387:14–20.
13. Hutchings L, Watkinson P, Young JD, Willett K. Defining multiple organ failure after major trauma: a comparison of the denver, sequential organ failure assessment, and Marshall scoring systems. J Trauma Acute Care Surg. 2017;82(3):534–41. https://doi.org/10.1097/TA.0000000000001328.
14. Padar M, Starkopf J, Uusvel G, Reintam Blaser A. Gastrointestinal failure affects outcome of intensive care. J Crit Care. 2019;2(52):103–8.
15. Reintam Blaser A, Poeze M, Malbrain ML, Björck M, Oudemans-van Straaten HM, Starkopf J. Gastro-Intestinal Failure Trial Group. Gastrointestinal symptoms during the first week of intensive care are associated with poor outcome: a prospective multicentre study. Intensive Care Med. 2013;39(5):899–909.
16. Deitch EA. Bacterial translocation or lymphatic drainage of toxic products from the gut: what is important in human beings? Surgery. 2002;131(3):241–4.
17. Vollmar B, Menger MD. Intestinal ischemia/reperfusion: microcirculatory pathology and functional consequences. Langenbeck's Arch Surg. 2011;396(1):13–29. https://doi.org/10.1007/s00423-010-0727-x.
18. Pironi L, Corcos O, Forbes A, Holst M, Joly F, Jonkers C, Klek S, Lal S, Blaser AR, Rollins KE, Sasdelli AS, Shaffer J, Van Gossum A, Wanten G, Zanfi C, Lobo DN, ESPEN Acute and Chronic Intestinal Failure Special Interest Groups. Intestinal failure in adults: recommendations from the ESPEN expert groups. Clin Nutr. 2018;37(6 Pt A):1798–809. https://doi.org/10.1016/j.clnu.2018.07.036.
19. Karcioglu O, Topacoglu H, Dikme O, Dikme O. A systematic review of the pain scales in adults: which to use? Am J Emerg Med. 2018;36(4):707–14. https://doi.org/10.1016/j.ajem.2018.01.008.
20. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, Duchesne J, Bjorck M, Leppaniemi A, Ejike JC, Sugrue M, Cheatham M, Ivatury R, Ball CG, Reintam Blaser A, Regli A, Balogh ZJ, D'Amours S, Debergh D, Kaplan M, Kimball E, Olvera C, Pediatric Guidelines Sub-Committee for the World Society of the Abdominal Compartment Syndrome. Intra-abdominal hypertension and the abdominal compartment syndrome: updated

consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 2013;39(7):1190–206. https://doi.org/10.1007/s00134-013-2906-z.
21. Reintam Blaser A, Parm P, Kitus R, Starkopf J. Intra-abdominal hypertension and gastrointestinal symptoms in mechanically ventilated patients. Crit Care Res Pract. 2011;2011:982507. https://doi.org/10.1155/2011/982507.
22. Reintam Blaser A, Regli A, De Keulenaer B, Kimball EJ, Starkopf L, Davis WA, Greiffenstein P, Starkopf J. Incidence, Risk Factors, and Outcomes of Intra-Abdominal (IROI) Study Investigators. Incidence, risk factors, and outcomes of intra-abdominal hypertension in critically ill patients-a prospective multicenter study (IROI Study). Crit Care Med. 2019;47(4):535–42. https://doi.org/10.1097/CCM.0000000000003623.
23. Reintam Blaser A, Deane AM. Normal physiology of the gastrointestinal system. In: Webb A, Angus D, Finfer S, Gattinoni L, Singer M, editors. Oxford textbook of critical care. 2nd ed; 2016. p. 811–4. https://doi.org/10.1093/med/9780199600830.003.0172. eISBN: 9780191810398.
24. Krishnasamy S, Abell TL. Diabetic gastroparesis: principles and current trends in management. Diab Ther. 2018;9(Suppl 1):1–42. https://doi.org/10.1007/s13300-018-0454-9.
25. Plummer MP, Reintam Blaser A, Deane AM. Gut dysmotility in the ICU: diagnosis and therapeutic options. Curr Opin Crit Care. 2019;25(2):138–44. https://doi.org/10.1097/MCC.0000000000000581.
26. Rauch S, Krueger K, Turan A, You J, Roewer N, Sessler DI. Use of wireless motility capsule to determine gastric emptying and small intestinal transit times in critically ill trauma patients. J Crit Care. 2012;27(5):534.e7–12. https://doi.org/10.1016/j.jcrc.2011.12.002.
27. Toumadre JP, Barclay M, Fraser R, Dent J, Young R, Berce M, Jury P, Fergusson L, Burnett J. Small intestinal motor patterns in critically ill patients after major abdominal surgery. Am J Gastroenterol. 2001;96(8):2418–26.
28. Zhuang CL, Chen FF, Lu JX, Zheng BS, Liu S, Zhou CJ, Huang DD, Shen X, Yu Z. Impact of different surgical traumas on postoperative ileus in rats and the mechanisms involved. Int J Clin Exp Med. 2015;8(9):16778–86.
29. Wierdsma NJ, Peters JH, Weijs PJ, Keur MB, Girbes AR, van Bodegraven AA, Beishuizen A. Malabsorption and nutritional balance in the ICU: fecal weight as a biomarker: a prospective observational pilot study. Crit Care. 2011;15(6):R264. https://doi.org/10.1186/cc10530.
30. Reignier J, Mercier E, Le Gouge A, Boulain T, Desachy A, Bellec F, Clavel M, Frat JP, Plantefeve G, Quenot JP, Lascarrou JB, Clinical Research in Intensive Care and Sepsis (CRICS) Group. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. JAMA. 2013;309(3):249–56. https://doi.org/10.1001/jama.2012.196377.
31. Reintam Blaser A, Starkopf J, Moonen PJ, Malbrain MLNG, Oudemans-van Straaten HM. Perioperative gastrointestinal problems in the ICU. Anaesthesiol Intens Ther. 2018;50(1):59–71. https://doi.org/10.5603/AIT.a2017.0064.
32. Perez-Calatayud AA, Carrillo-Esper R, Anica-Malagon ED, Briones-Garduño JC, Arch-Tirado E, Wise R, Malbrain MLNG. Point-of-care gastrointestinal and urinary tract sonography in daily evaluation of gastrointestinal dysfunction in critically ill patients (GUTS Protocol). Anaesthesiol Intens Ther. 2018;50(1):40–8. https://doi.org/10.5603/AIT.a2017.0073.
33. Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, Casaer MP, Deane AM, Fruhwald S, Hiesmayr M, Ichai C, Jakob SM, Loudet CI, Malbrain ML, Montejo González JC, Paugam-Burtz C, Poeze M, Preiser JC, Singer P, van Zanten AR, De Waele J, Wendon J, Wernerman J, Whitehouse T, Wilmer A, Oudemans-van Straaten HM, ESICM Working Group on Gastrointestinal Function. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. Intensive Care Med. 2017;43(3):380–98. https://doi.org/10.1007/s00134-016-4665-0.
34. Reintam Blaser A, Starkopf J, Kirsimägi Ü, Deane AM. Definition, prevalence, and outcome of feeding intolerance in intensive care: a systematic review and meta-analysis. Acta Anaesthesiol Scand. 2014;58(8):914–22. https://doi.org/10.1111/aas.12302.

35. Heyland DK, Ortiz A, Stoppe C, Patel JJ, Yeh DD, Dukes G, Chen YJ, Almansa C, Day AG. Incidence, risk factors, and clinical consequence of enteral feeding intolerance in the mechanically ventilated critically ill: an analysis of a multicenter, multiyear database. Crit Care Med. 2021;49(1):49–59. https://doi.org/10.1097/CCM.0000000000004712.
36. Reintam Blaser A, Deane AM, Preiser JC, Arabi YM, Jakob SM. Enteral feeding intolerance: updates in definitions and pathophysiology. Nutr Clin Pract. 2021;36(1):40–9. https://doi.org/10.1002/ncp.10599.
37. Virani FR, Peery T, Rivas O, Tomasek J, Huerta R, Wade CE, Lee J, Holcomb JB, Uray K. Incidence and effects of feeding intolerance in trauma patients. JPEN J Parenter Enteral Nutr. 2018;43:742. https://doi.org/10.1002/jpen.1469).
38. Nassar AP Jr, da Silva FM, de Cleva R. Constipation in intensive care unit: incidence and risk factors. J Crit Care. 2009;24(4):630.e9–12. https://doi.org/10.1016/j.jcrc.2009.03.007.
39. Assimakopoulos SF, Triantos C, Thomopoulos K, Fligou F, Maroulis I, Marangos M, Gogos GA. Gut-origin sepsis in the critically ill patient: pathophysiology and treatment. Infection. 2018;46:751–60.
40. Reintam Blaser A, Deane AM, Fruhwald S. Diarrhoea in the critically ill. Curr Opin Crit Care. 2015;21(2):142–53. https://doi.org/10.1097/MCC.0000000000000188.
41. Jakob SM, Bütikofer L, Berger D, Coslovsky M, Takala J. A randomized controlled pilot study to evaluate the effect of an enteral formulation designed to improve gastrointestinal tolerance in the critically ill patient-the SPIRIT trial. Crit Care. 2017;21(1):140. https://doi.org/10.1186/s13054-017-1730-1.
42. Gangadhar K, Kielar A, Dighe MK, O'Malley R, Wang C, Gross JA, Itani M, Lalwani N. Multimodality approach for imaging of non-traumatic acute abdominal emergencies. Abdom Radiol (NY). 2016;41(1):136–48. https://doi.org/10.1007/s00261-015-0586-6.
43. Krajewski K, Siewert B, Eisenberg RL. Colonic dilation. AJR Am J Roentgenol. 2009;193:363–72. https://doi.org/10.2214/AJR.09.3353.
44. Savarino E, Savarino V, Fox M, Di Leo G, Furnari M, Marabotto E, Gemignani L, Bruzzone L, Moscatelli A, De Cassan C, Sardanelli F, Sconfienza LM. Measurement of oro-caecal transit time by magnetic resonance imaging. Eur Radiol. 2015;25(6):1579–87. https://doi.org/10.1007/s00330-014-3575-1.
45. Peoc'h K, Nuzzo A, Guedj K, Paugam C, Corcos O. Diagnosis biomarkers in acute intestinal ischemic injury: so close, yet so far. Clin Chem Lab Med. 2018;56(3):373–85. https://doi.org/10.1515/cclm-2017-0291.
46. Treskes N, Persoon AM, van Zanten ARH. Diagnostic accuracy of novel serological biomarkers to detect acute mesenteric ischemia: a systematic review and meta-analysis. Intern Emerg Med. 2017;12(6):821–36. https://doi.org/10.1007/s11739-017-1668-y.
47. Crenn P, Vahedi K, Lavergne-Slove A, et al. Plasma citrulline: a marker of enterocyte mass in villous atrophy-associated small bowel disease. Gastroenterology. 2003;124(5):1210–9.
48. Crenn P, Messing B, Cynober L. Citrulline as a biomarker of intestinal failure due to enterocyte mass reduction. Clin Nutr. 2008;27(3):328–39. https://doi.org/10.1016/j.clnu.2008.02.005.
49. Levy B, Gawalkiewicz P, Vallet B, Briancon S, Nace L, Bollaert PE. Gastric capnometry with air-automated tonometry predicts outcome in critically ill patients. Crit Care Med. 2003;31(2):474–80. https://doi.org/10.1097/01.CCM.0000050445.48656.28.
50. Moonen PJ, Reintam Blaser A, Starkopf J, Oudemans-van Straaten HM, Van der Mullen J, Vermeulen G, Malbrain MLNG. The black box revelation: monitoring gastrointestinal function. Anaesthesiol Intens Ther. 2018;50(1):72–81. https://doi.org/10.5603/AIT.a2017.0065.
51. Burmeister DM, Johnson TR, Lai Z, Scroggins SR, DeRosa M, Jonas RB, Zhu C, Scherer E, Stewart RM, Schwacha MG, Jenkins DH, Eastridge BJ, Nicholson SE. The gut microbiome distinguishes mortality in trauma patients upon admission to the emergency department. J Trauma Acute Care Surg. 2020;88(5):579–87. https://doi.org/10.1097/TA.0000000000002612.
52. Lankelma JM, van Vught LA, Belzer C, Schultz MJ, van der Poll T, de Vos WM, Wiersinga WJ. Critically ill patients demonstrate large interpersonal variation in intestinal microbiota dysregulation: a pilot study. Intensive Care Med. 2017;43(1):59–68. https://doi.org/10.1007/s00134-016-4613-z.

53. Ojima M, Shimizu K, Motooka D, Ishihara T, Nakamura S, Shintani A, Ogura H, Iida T, Yoshiya K, Shimazu T. Gut dysbiosis associated with antibiotics and disease severity and its relation to mortality in critically ill patients. Dig Dis Sci. 2021;3:1–13. https://doi.org/10.1007/s10620-021-07000-7.
54. Balihar K, Kotyza J, Zdrhova L, Kozeluhova J, Krcma M, Matejovic M. Characterization of esophageal motor activity, gastroesophageal reflux, and evaluation of prokinetic effectiveness in mechanically ventilated critically ill patients: a high-resolution impedance manometry study. Crit Care. 2021;25(1):54. https://doi.org/10.1186/s13054-021-03479-8.
55. Ince C, Ertmer C. Hemodynamic coherence: its meaning in perioperative and intensive care medicine. Best Pract Res Clin Anaesthesiol. 2016;30(4):395–7. https://doi.org/10.1016/j.bpa.2016.11.004.
56. Ince C, Boerma EC, Cecconi M, De Backer D, Shapiro NI, Duranteau J, Pinsky MR, Artigas A, Teboul JL, Reiss IKM, Aldecoa C, Hutchings SD, Donati A, Maggiorini M, Taccone FS, Hernandez G, Payen D, Tibboel D, Martin DS, Zarbock A, Monnet X, Dubin A, Bakker J, Vincent JL, Scheeren TWL. Cardiovascular Dynamics Section of the ESICM. Second consensus on the assessment of sublingual microcirculation in critically ill patients: results from a task force of the European Society of Intensive Care Medicine. Intensive Care Med. 2018;44(3):281–99. https://doi.org/10.1007/s00134-018-5070-7.
57. Myles PS, Bellomo R, Corcoran T, Forbes A, Peyton P, Story D, Christophi C, Leslie K, McGuinness S, Parke R, Serpell J, Chan MTV, Painter T, McCluskey S, Minto G, Wallace S. Australian and New Zealand College of Anaesthetists Clinical Trials Network and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Restrictive versus liberal fluid therapy for major abdominal surgery. N Engl J Med. 2018;378(24):2263–74. https://doi.org/10.1056/NEJMoa1801601.
58. Kar P, Jones KL, Plummer MP, Ali Abdelhamid Y, Giersch EJ, Summers MJ, Hatzinikolas S, Heller S, Horowitz M, Deane AM. Antecedent hypoglycemia does not attenuate the acceleration of gastric emptying by hypoglycemia. J Clin Endocrinol Metab. 2017;102(11):3953–60. https://doi.org/10.1210/jc.2017-00051.
59. Brigode WM, Jones C, Vazquez DE, Evans DC. Scrutinizing the evidence linking hypokalemia and ileus: a commentary on fact and dogma. Int J Acad Med. 2015;1:21–6.
60. Fruhwald S, Holzer P. Gastrointestinal motility drugs in critical illness. In: Webb A, Angus D, Finfer S, Gattinoni L, Singer M, editors. Oxford textbook of critical care. 2nd ed. Oxford: Oxford University Press; 2016. p. 175–80.
61. Wallström A, Frisman GH. Facilitating early recovery of bowel motility after colorectal surgery: a systematic review. J Clin Nurs. 2014;23(1–2):24–44. https://doi.org/10.1111/jocn.12258.
62. Malbrain ML, Viaene D, Kortgen A, De Laet I, Dits H, Van Regenmortel N, Schoonheydt K, Bauer M. Relationship between intra-abdominal pressure and indocyanine green plasma disappearance rate: hepatic perfusion may be impaired in critically ill patients with intra-abdominal hypertension. Ann Intensive Care. 2012;2(Suppl 1):S19.
63. Taylor BE, McClave SA, Martindale RG, Warren MM, Johnson DR, Braunschweig C, McCarthy MS, Davanos E, Rice TW, Cresci GA, Gervasio JM, Sacks GS, Roberts PR, Compher C. Society of Critical Care Medicine; American Society of Parenteral and Enteral Nutrition. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). Crit Care Med. 2016;44(2):390–438. https://doi.org/10.1097/CCM.0000000000001525.
64. Doig GS, Heighes PT, Simpson F, Sweetman EA. Early enteral nutrition reduces mortality in trauma patients requiring intensive care: a meta-analysis of randomised controlled trials. Injury. 2011;42(1):50–6. https://doi.org/10.1016/j.injury.2010.06.008.
65. Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, Bellingan G, Leonard R, Mythen MG, Rowan KM, CALORIES Trial Investigators. Trial of the route of early nutritional support in critically ill adults. N Engl J Med. 2014;371(18):1673–84. https://doi.org/10.1056/NEJMoa1409860.

66. Reignier J, Boisramé-Helms J, Brisard L, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet. 2018;13:391133–43.
67. Braunschweig CA, Sheean PM, Peterson SJ, Gomez Perez S, Freels S, Lateef O, Gurka D, Fantuzzi G. Intensive nutrition in acute lung injury: a clinical trial (INTACT). JPEN J Parenter Enteral Nutr. 2015;39(1):13–20. https://doi.org/10.1177/0148607114528541.
68. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, Van Cromphaut S, Ingels C, Meersseman P, Muller J, Vlasselaers D, Debaveye Y, Desmet L, Dubois J, Van Assche A, Vanderheyden S, Wilmer A, Van den Berghe G. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506–17. https://doi.org/10.1056/NEJMoa1102662.
69. Fraipont V, Preiser JC. Energy estimation and measurement in critically ill patients. JPEN J Parenter Enteral Nutr. 2013;37(6):705–13.
70. Gunst J, Van den Berghe G. Parenteral nutrition in the critically ill. Curr Opin Crit Care. 2017;23(2):149–58. https://doi.org/10.1097/MCC.0000000000000385.
71. Singer P, Reintam Blaser A, Berger MM, Alhazzani W, Calder PC, Casaer MP, Hiesmayr M, Mayer K, Montejo JC, Pichard C, Preiser JC, van Zanten ARH, Oczkowski S, Szczeklik W, Bischoff SC. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr. 2019;38(1):48–79. https://doi.org/10.1016/j.clnu.2018.08.037.
72. Arabi YM, Aldawood AS, Haddad SH, et al. Permissive underfeeding or standard enteral feeding in critically ill adults. N Engl J Med. 2015;372(25):2398–408.
73. Rice TW, Mogan S, Hays MA, Bernard GR, Jensen GL, Wheeler AP. Randomized trial of initial trophic versus full-energy enteral nutrition in mechanically ventilated patients with acute respiratory failure. Crit Care Med. 2011;39(5):967–74.
74. Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, Thibault R, Pichard C. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet. 2013;381(9864):385–93. https://doi.org/10.1016/S0140-6736(12)61351-8.
75. Reintam Blaser A, Preiser JC, Fruhwald S, Wilmer A, Wernerman J, Benstoem C, Casaer MP, Starkopf J, van Zanten A, Rooyackers O, Jakob SM, Loudet CI, Bear DE, Elke G, Kott M, Lautenschläger I, Schäper J, Gunst J, Stoppe C, Nobile L, Fuhrmann V, Berger MM, Oudemans-van Straaten HM, Arabi YM, Deane AM, Working Group on Gastrointestinal Function within the Section of Metabolism, Endocrinology and Nutrition (MEN Section) of ESICM. Gastrointestinal dysfunction in the critically ill: a systematic scoping review and research agenda proposed by the Section of Metabolism, Endocrinology and Nutrition of the European Society of Intensive Care Medicine. Crit Care. 2020;24(1):224. https://doi.org/10.1186/s13054-020-02889-4.

Post-injury Kidney Failure

15

Andrew Nguyen, Arnold Tabuenca, and Raul Coimbra

15.1 Definitions of Acute Kidney Injury

Qualitatively, renal failure describes the loss of the kidney's various fluid and solute management processes. Quantitatively, however, specific definitions have been developed for renal insufficiency.

Chronic kidney disease (CKD) describes a long-term impairment in kidney function beyond 3 months duration. Previously, staging of kidney disease was based solely on glomerular filtration rate (GFR) [1]. The KDIGO group (Kidney Disease Improving Global Outcomes) now classifies CKD based on the aggregate of three domains: underlying cause, GFR category, and albuminuria category (CGA). The aggregate of these three descriptors is the CKD staging. This more descriptive staging strategy reflects the prognostic and treatment implications that the underlying disease and albuminuria convey. CKD requiring renal replacement therapy (dialysis) is described as End-Stage Renal Disease (Tables 15.1, 15.2, and 15.3).

While acute renal failure is the abrupt decline of kidney function, its definition has been more difficult. Over the past decades, more than 35 separate definitions of acute kidney disease have been described [2].

A. Nguyen · A. Tabuenca · R. Coimbra (✉)
Riverside University Health System Medical Center, Loma Linda University School of Medicine, Loma Linda, CA, USA
e-mail: andrew.nguyen2@ruhealth.org; a.tabuenca@ruhealth.org; r.coimbra@ruhealth.org

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_15

Table 15.1 GFR categories in Chronic Kidney Disease (adapted from the KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int (Suppl.) 2013;3:1–150)

GFR category	GFR (mL/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Table 15.2 Albuminuria categories in Chronic Kidney Disease (adapted from the KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int (Suppl.) 2013;3:1–150)

Albuminuria category	Albumin excretion rate (mg/24 h)	Terms
A1	<30	Normal to mildly increased
A2	30–300	Moderately increased
A3	>300	Severely increased

Table 15.3 Prognosis of CKD by Stage (Green—low risk if no other markers of kidney disease; Yellow—moderate risk; Orange—high risk; Red—very high risk) (adapted from the KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int (Suppl.) 2013;3:1–150)

		Albuminuria category		
		A1	A2	A3
GFR category	G1	G1 A1	G1 A2	G1 A3
	G2	G2 A1	G2 A2	G2 A3
	G3a	G3a A1	G3a A2	G3a A3
	G3b	G3b A1	G3b A2	G3b A3
	G4	G4 A1	G4 A2	G4 A3
	G5	G5 A1	G5 A2	G5 A3

One early definition for the trauma population was proposed by the American College of Surgeons' Committee on Trauma (ACSCOT) and defined acute renal failure (ARF) as a serum creatinine ≥3.5, blood urea nitrogen (BUN) >100, or the need for renal replacement therapy [3].

In May 2004, the Acute Dialysis Quality Initiative (ADQI) Group proposed the RIFLE classification scheme (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; Table 15.4) [4]. The system utilized serum creatinine, GFR, or urine output to describe the severity of renal impairment. It also codified the notion of renal dysfunction as a spectrum of disease, with the terminology acute kidney injury (AKI) replacing acute renal failure (ARF). RIFLE was found to have good clinical correlation, with an independent and stepwise increase in mortality as

severity of acute kidney injury increased. Patients with RIFLE class R are at risk of progressing to class I or F and have an increase in hospital length of stay [5]. The RIFLE criteria were limited, however, by its reliance on baseline serum creatinine, which often was not known for an acute patient. Attempts to utilize the Modification of Diet in Renal Disease Study (MDRD) equation to estimate baseline renal function were limited by the equations' overestimation of acute renal failure [6].

Three years later, in March 2007, the Acute Kidney Injury Network (AKIN) proposed a modified version of the RIFLE criteria (Table 15.5) [7]. The revised criteria encompassed elevations of creatinine above baseline, as well as absolute elevations in creatinine or decrease in urine output. The AKIN definition is considered after adequate hydration and requires two serum creatinine measurements within 48 h. Its non-reliance on baseline serum creatinine and its provision for adequate resuscitation adds clinical context. In the trauma population, the AKIN modification was found to increase the capture of acute renal failure in comparison to the ACSCOT definition. Patients meeting AKIN criteria had longer ICU and hospital length of stay and had increased incidence of multiple organ failure and death [3]. A limitation of the AKIN definition lies in its specification of creatinine measurements within 48 h. It thus does not recognize AKI when creatinine elevation occurs beyond 48 h. Also, the definition of AKIN Stage 3 includes the utilization of renal replacement therapy, and there is variability for the initiation of renal replacement therapy in clinical practice.

Table 15.4 The 2004 Acute Dialysis Quality Initiative (ADQI) RIFLE classification scheme for acute kidney injury (adapted from Bellomo R, et al. Acute renal failure: definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204–12)

	GFR criteria	Urine output criteria
Risk	Increased serum creatinine × 1.5 or GFR decrease >25%	UO <0.5 mL/kg/h × 6 h
Injury	Increased serum creatinine × 2 or GFR decrease >50%	UO <0.5 mL/kg/h × 12 h
Failure	Increased serum creatinine × 3, GFR decrease 75%, or serum creatinine ≥4 mg/dL (or acute rise ≥0.5 mg/dL)	UO <0.3 mL/kg/h × 24 h or Anuria × 12 h
Loss	Persistent acute renal failure (complete loss of kidney function >4 weeks)	
ESKD	End-stage kidney disease (>3 months)	

Table 15.5 The 2007 Acute Kidney Injury Network (AKIN) modification of RIFLE criteria for AKI (adapted from Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31)

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine ≥0.3 mg/dL or increase to more than or equal to 150–200% from baseline	<0.5 mL/kg/h for more than 6 h
2	Increase in serum creatinine to more than 200–300% from baseline	<0.5 mL/kg/h for more than 12 h
3	Increase in serum creatinine to more than 300% from baseline (or serum ≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL)	<0.3 mL/kg/h for 24 h or anuria for 12 h

Table 15.6 Current disease staging in Acute Kidney Injury (adapted from the KDIGO 2012 Clinical Practice Guideline for Acute Kidney Injury. Kidney Int. Suppl. 2012;2:1–138)

Stage	Serum creatinine criteria	Urine output criteria
1	1.5–1.9 times baseline OR ≥0.3 mg/dL increase	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	≥3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dL OR Initiation of renal replacement therapy OR In patients <18 years, decrease in eGFR to <35 mL/min/1.73 m^2	<0.3 mL/kg/h for ≥24 h OR anuria for ≥12 h

The most recent consensus definition of acute kidney injury was released by the Kidney Disease: Improving Global Outcomes (KDIGO) group [8] and defines a state of AKI as:

- Increase in serum creatinine by ≥0.3 mg/dL within 48 h;
- or increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days;
- or urine volume <0.5 mL/kg/h for 6 h.

Once AKI is identified, it can be staged on a scale of 1–3 (Table 15.6).

A multi-national cross-sectional study has validated the KDIGO definition for the general ICU population, noting that increases in AKI severity under the revised definition were associated with significant stepwise increases in mortality. Patients with AKI had worse kidney function at discharge in comparison to those without AKI [9].

AKI, a description of the level of renal impairment, should be differentiated from acute tubular necrosis (ATN), which lacks the same consensus definition as AKI. During the Second World War, the syndrome of renal failure was described and correlated with histologic finding of tubular necrosis [10]. Thus, for a time, ATN and ARF were used interchangeably. While ATN now has a histologic description, only a small minority of patients undergo biopsy and pathologic review. Instead, ATN has an alternate clinical description: a state during which there is adequate renal perfusion to maintain the renal tubules, but insufficient to maintain glomerular filtration. Thus, in today's era, only a few "ATN" patients will have true widespread renal parenchymal tissue necrosis [8].

15.2 Background and Incidence

15.2.1 Characteristics of the AKI Population

The prevalence of acute kidney injury in the trauma population ranges from less than 1% to more than 26%, though variation in the definition of AKI makes comparison difficult [11–13]. AKI within trauma patients admitted to an ICU can range

from 24% to 50% [14, 15]. Within the military population, rates of AKI seem to fall within the above rates. A review of US military casualties between 2002 and 2011 in Iraq and Afghanistan showed a 12.5% rate of AKI [16]. A more limited review for the military ICU population between 2012 and 2013 for the same conflict showed an AKI rate of 34.3% [17]. Some reviews suggest that the typical patient with AKI is older than non-AKI patients (median age 63 vs. 53 in a study of patients from Southern Taiwan [18] and mean age 47 vs. 41 in a review of the Inflammation and the Host Response to Injury NIH database [13]). Frequently, patients with AKI are male, with the two prior studies showing 71.8% and 70% males, respectively [13, 18].

15.2.2 Injury Severity

Patients with AKI tend to have more injuries. The retrospective review of southern Taiwanese trauma patients showed an ISS of 19.8 in those with AKI, while non-AKI patients had an ISS of 8.9 [18]. That study also showed that patients with AKI had higher rates of head and neck, thoracic, and abdominal injury. Those patients also had higher rates of intracranial hemorrhage, liver injury, and rhabdomyolysis. Patients without AKI, in contrast, had higher rates of extremity injury [18]. Multiple studies have shown AKI to be associated with worse mortality in the trauma population. AKI patients also tended to have higher rates of ICU admission and total hospital length of stay.

The AKI population also exhibits, on average, decreased level of GCS [18]. These patients also have worse hemodynamic markers, tending towards worse hypotension, tachycardia, and tachypnea. Patients also exhibited worse anemia. AKI patients tended to have increased rates of invasive emergency department procedures, including cardiopulmonary resuscitation, mechanical ventilation, chest tube insertion, and blood transfusion.

15.2.3 Association of Shock and AKI

While a precise correlation between shock in the setting of trauma and AKI is not completely studied, patients with AKI do tend towards hypotension, elevated lactate, and need for packed red blood cell transfusion [13]. More aggressive volume resuscitation does seem to decrease the incidence of AKI [19].

15.2.4 Genetics and Pre-existing Conditions

In the 1990s, it became increasingly clear that pre-existing conditions contributed to traumatic acute kidney injury. One early trauma study that identified renal failure by ICD-9 coding noted that 40% of patients had a pre-existing condition. It appeared that this group had diminished physiologic reserve: patients tended to be older but

less injured than those without prior medical problems. Despite this, the additional insult of post-traumatic renal failure produced a 77% multi-organ failure rate and a mortality rate of 88% [11].

More contemporary studies show that patients with AKI have higher rates of diabetes, hypertension, coronary artery disease, and cerebrovascular disease [18]. Patients with AKI also tend towards obesity [20]. AKI is also more common in African Americans, though the mechanism for this is poorly understood [20]. AKI is more common in those with blood type A, suggesting that ABO glycans play a role in AKI susceptibility [19]. A Japanese study associated post-traumatic AKI with the elderly and those with chronic kidney disease [21].

Thus, it appears that organ crosstalk and inter-organ connectivity may play a role in worsening organ failure after trauma. The exact mechanism by which this occurs remains to be elucidated. Independent of the cause, it appears that pre-existing conditions exacerbate acute kidney injury and further contribute to post-traumatic mortality [22, 23].

15.2.5 Relationship with Other Organ Systems

The kidney maintains significant endocrine functions that can be disrupted with organ failure [24]. One area is fluid balance. Renin is produced by the juxtaglomerular apparatus in response to a decrease in arterial blood pressure, decrease in sodium concentration, or increase in catecholamines. Renin goes on to cleave angiotensinogen to angiotensin I; angiotensin I is converted to angiotensin II by the enzyme ACE (angiotensin-converting enzyme). The results in an increase in antidiuretic hormone production and aldosterone secretion. The final effect is systemic vasoconstriction and renal sodium and water reabsorption.

Other endocrine functions include hematopoiesis, calcium/phosphorus metabolism, blood glucose management, and even some control of gastric acid production. The renal cortex produces erythropoietin in response to hypoxia, thus stimulating bone marrow production of red blood cells. Calcium homeostasis involves both the liver and kidney. After liver conversion of Vitamin D3 into the $25(OH)D_3$ form, 1-alpha hydrolase (produced by the renal proximal tubule) converts it into the active form of 1-alpha,$25(OH)_2D_3$. This active form of Vitamin D induces calcium release from bone tissue and calcium absorption from the gut. Meanwhile, parathyroid hormone induces the kidney to absorb calcium and reduce phosphorus absorption. The kidney, furthermore, is the primary site of insulin degradation. Insulin is filtered from the systemic circulation via proximal tubular reabsorption and glomerular filtration. The kidney also appears to metabolize gastrin, and excess gastrin in renal failure patients may contribute to peptic ulcer disease.

In addition to its endocrine function, there are other organ crosstalk effects that are still being explored [25, 26]. Renal impairment and thus fluid overload can affect lung function by inducing pulmonary edema, but circulating cytokines

including interleukin (IL)-6 and IL-8 can induce lung inflammation and injury. Renal dysfunction can also affect the heart, with 60% of AKI patients also developing heart failure. These effects appear to have a long-term component: even patients who recovered from dialysis-requiring AKI had higher long-term risks of coronary events. Neurologic function can be compromised by uremic toxins, inducing seizures, altered mental status, and decreased attention. And while hepatorenal syndrome describes kidney dysfunction secondary to liver disease, it appears the reverse may be true also: AKI-related toxic metabolites can negatively influence liver function, though the exact interaction remains an area of study.

Thus, renal failure can begin a cascade of organ dysfunction throughout the body. While exact mechanisms remain to be elucidated, the area of study brings potential for future areas of treatment and disease management.

15.2.6 Mortality Rates

The correlation between renal failure and mortality is well established. In the general ICU population, despite improvements in the management of acute renal failure, mortality rates have tended towards about 50% [27]. This mortality rate, in particular, is despite the use of various renal replacement therapies [28]. At time of hospital discharge, 5–20% of these AKI patients remain dialysis dependent [28].

In trauma patients requiring ICU admission, the development of renal failure within the first 24 h is an independent risk factor for mortality. In a study of 1044 Scandinavian trauma patients admitted to the ICU, those with renal failure were 30-times more likely to have in-ICU mortality compared to their non-renal failure counterparts [29]. In Australia and New Zealand, it was shown that worsening degree of renal failure was also associated with increased mortality in a stepwise fashion [30].

High mortality was also present in post-traumatic renal failure patients not admitted to the ICU. Morality rates in the civilian trauma population with AKI have been reported as high as 27–38% [12, 23], with those patients having three times the risk of death compared to the baseline trauma population [13]. The combat casualty population exhibits a similar behavior, with the mortality rate with AKI being 13.1–21.5% versus 1.5–2.3% for non-AKI patients [16, 31].

15.3 Individual Causes and Specific Management

The causes of acute kidney injury in the trauma population are often multifactorial. Historically, renal insufficiency has been described as prerenal, intrinsic renal, or post-renal [27]. This description is useful as it correlates to the underlying root cause of renal failure.

15.3.1 Prerenal Causes of Renal Failure

15.3.1.1 Hypovolemia and Hemorrhagic Shock

The kidneys together utilize 20–25% of cardiac output under normal conditions but extract only 10% of oxygen from the blood [32]. Blood flow into and beyond the glomerulus is regulated by afferent and efferent arteriole tone. While some effluent is forced out of the glomerulus and into the renal tubules for solute management, un-excreted blood continues beyond the glomerulus to provide oxygenation for the nephron. In the setting of trauma, hypovolemia leads to decreased renal perfusion pressure. At the expense of post-glomerular oxygen delivery, the renin–angiotensin–aldosterone axis is activated to maintain afferent and efferent arteriole tone. Thus, while overall renal blood flow and oxygenation is decreased, glomerular filtration is preserved. Renal oxygen demand of the nephron, however, remains high to support sodium reuptake and volume retention. As arterial pressure continues to fall, loss of autoregulation results in renal ischemia and decreased glomerular filtration. For trauma patients, this is the most common cause of renal insufficiency [27]. In the setting of hemorrhage, loss of oxygen carrying capacity can further ischemic insults to the kidney [33]. Renal hypoperfusion may be exacerbated by further vasoconstriction, which can be mediated by prostanoids, cytokines, and vasopressors [27]. At the biochemical level, low tissue oxygenation induces the expression of hypoxia-inducible factor-1a (HIF-1a), which is an adaptive protein for hypoxia. With continued hypoxia, there is the loss of the tubule brush border and desquamation of tubular cells into the tubular lumen. These changes mark a histologic presence of acute tubular necrosis. With resuscitation and restoration of oxygen delivery, oxygen-free radicals are produced, while superoxide dismutase activity drops, thus triggering cell apoptosis. Other biochemical mediators implicated in renal injury include nuclear factor-Kappa B, tumor necrosis factor-α, and IL-6. Experimentally, lowering oxidative stress improves renal function and creatinine clearance [33].

Completeness of resuscitation remains at the vanguard of treating patients in the prerenal state.

Alfred Blalock in the 1930s identified shock as a state of hypovolemia; previous to this it was thought that shock was brought on by circulating toxins [34]. By the Vietnam War era, it was recognized that simply returning blood volume to a bleeding patient was insufficient. Owing to the "third spacing" of fluid, trauma patients required additional resuscitation beyond their acute blood loss amount. An early study highlighted the declining incidence of traumatic renal failure between the 1950s and 1980s, possibly owing to the improved resuscitation between these eras [35]. Another study in trauma patients compared the first and second 10-year periods between 1972 and 1991. It was noted that with improved resuscitation (as well as improved trauma care overall), renal failure rates dropped from 8.4% to 3.7% and mortality improved from 37% to 22% [36]. This gave rise to an era of large-volume crystalloid resuscitation. It was noted that resuscitation with a balanced solution, such as Plasmalyte, may result in decreased hyperchloremic acidosis but it was unclear if renal function or mortality were improved [33]. It became clear, however, that over-resuscitation led to significant problems, including acute respiratory

distress syndrome, abdominal compartment syndrome, and mortality. Investigations began into alternatives to crystalloid solutions, such as synthetic colloids and hypertonic saline. Resuscitation with hydroxyethyl starch (HES) solutions, a synthetic colloid, theoretically maintains oncotic pressure. Multiple studies, including those specific to trauma patients, have demonstrated an association between HES and renal failure. The use of HES is no longer recommended [22]. Investigations into hypotonic saline showed early mortality in trauma patients and overall no better outcomes in comparison to standard fluids [37].

Currently, the focus on trauma resuscitation has now transitioned towards a damage-control-resuscitation strategy, with relative permissive hypotension (especially in penetrating trauma) until bleeding control is obtained. Additionally, the fluid of choice has transitioned to early administration of blood, though there have been relatively few trial data to guide this. There has arisen, however, a focus on giving whole blood if possible. Giving whole blood has been standard practice in the military, though it had not been well studied in the civilian setting. In 2011, a civilian retrospective cohort study with 353 massively transfused trauma patients compared unrefrigerated whole blood to standard fractionated units. The whole blood group had better coagulation laboratory markers but there was no difference in amount of blood transfused or mortality [38]. Military studies regarding fresh whole blood have been conflicting [39, 40].

The debate regarding whole blood continues. In 2013, a civilian randomized trial of 107 trauma patients was published. Patients were randomized between modified whole blood (leukocyte depleted cold-stored whole blood) versus component therapy. There was no difference in overall transfusion volumes. In subgroup analysis of patients without traumatic brain injury, however, the modified whole blood group demonstrated less transfusion volume [41]. The optimal level and method of resuscitation remains to be clarified.

15.3.1.2 Hypovolemia and Sepsis in the Trauma Patient

While severity of injury often dictates early mortality in trauma (including on-scene deaths and mortality within the first 24-h at a trauma center), sepsis represents a significant aspect of late ("trimodal") deaths in the trauma population. A cornerstone of sepsis management is early utilization of antibiotics and appropriate source control. Early work by Shoemaker in the 1980s and 1990s suggested that attaining optimal physiologic parameters for oxygen delivery would decrease mortality in critically ill patients [42]. From this developed the notion of goal-directed therapy, including volume expansion guided by central venous pressure and vasopressors to attain adequate blood pressure. Rivers' seminal 2001 study suggested that early application of goal-directed therapy was key to improved outcomes [43]. Subsequent randomized controlled trials of early goal-directed therapy vs. "usual care" (ARISE, ProCESS, and ProMISe) failed to show improvement in mortality [44–46]. While a criticism of these trials is that even "usual care" patients are receiving improved resuscitation than in the past, it appears that large-volume resuscitation to attain central venous pressure goals and central or mixed venous oxygenation values in of themselves do not lend to improved mortality. While undoubtedly volume

resuscitation remains important, the optimal physiologic marker remains to be seen. As a result, the 2016 surviving sepsis campaign guidelines recommend frequent reassessment of volume status [47]. Volume status can be assessed by passive leg raise, cardiac ultrasonography, and pulse-pressure or stroke volume variation in mechanically ventilated patients.

15.3.1.3 Abdominal Compartment Syndrome

Abdominal compartment syndrome can create a prerenal condition similar to shock. Kron et al. published a series in 1983 of post-operative patients that developed increased abdominal pressure (as evidenced by bladder-pressure measurements) as well as new onset renal failure. The patients' renal failure resolved with re-laparotomy and abdominal decompression. We now define abdominal compartment syndrome as bladder-pressure measurements higher than 20 mmHg with new-organ failure. Abdominal compartment syndrome may be present in an upwards of 37% of trauma patients, with pelvic or abdominal injuries leading to a rise in intra-abdominal pressure. In rare cases, patients without intraabdominal injury can get abdominal compartment syndrome due to large-volume resuscitation. Fluid resuscitation volume has been linked to the risk of abdominal compartment syndrome in trauma patients, as well as trauma patient mortality [48, 49]. The proportion of compartment syndrome patients with AKI has been reported to be 42%.

Several hypotheses have been proposed in regard to the underlying pathophysiology for abdominal compartment syndrome. One hypothesis is that abdominal pressure causes external renal parenchymal compression, thus leading to decreased renal perfusion pressure and decreased glomerular filtration rate (GFR). A 1982 study used anesthetized dogs in which intra-peritoneal bags were inflated to simulate abdominal compartment syndrome. As intra-abdominal pressure increased, cardiac output, renal blood flow, and glomerular filtration rate all decreased. Volume expansion corrected cardiac output, but renal blood flow and GFR remained low. This suggested that compartment syndrome was not related to cardiac output changes, but to the local pressure surrounding the retroperitoneum [50]. It appears, however, that compression of the kidney itself is not sufficient to cause compartment syndrome. A 2000 study using a swine model demonstrated that external renal compression did not decrease GFR or renal artery flow [51]. Instead, it appears that venous compression is the underlying pathophysiology. A separate swine model study from the same group showed that increasing pressure on the renal vein produced the characteristic decrease in GFR and renal artery flow [52].

Regardless of the underlying cause, the World Society of the Abdominal Compartment Syndrome recommends use of bladder pressure to measure intra-abdominal pressure. Decompressive laparotomy is the historical and recommended therapy for overt abdominal compartment syndrome. In a subgroup analysis of patients with non-traumatic brain injury, it was found that neuromuscular blockade decreased intra-abdominal pressure (as well as intracranial pressure) [53]. Thus, brief trials of neuromuscular blockade are permissible as a temporizing measure. Enteral decompression with nasogastric or rectal tubes may be beneficial. In settings of large amount of ascites contributing to abdominal pressure, percutaneous drainage is reasonable [54].

15.3.1.4 Respiratory Compromise as a Cause of Renal Failure

Respiratory failure can influence renal failure by several mechanisms. Severe hypoxemia (PaO_2 <40 mmHg) can lead to reduced renal blood flow and renal insufficiency. Though the evidence is less clear in mild hypoxia, even a smaller reduction in PaO_2 can induce renal dysfunction. Additionally, mechanical ventilation induces an increase in intra-thoracic pressure, initiating a decrease in cardiac preload and an increase in right-heart afterload. The resulting decrease in cardiac output decreases renal perfusion. Elevated levels of positive end-expiratory pressure (PEEP) can exacerbate this effect. Furthermore, inflammatory mediators released from the lung due to intrinsic lung disease and mechanical ventilation can enter the systemic circulation and compound renal failure [55].

15.3.1.5 Traumatic Brain Injury

The use of mannitol in traumatic brain injury deserves specific mention. AKI can be present in as much as 23% of patients with traumatic brain injury [56]. Patients with AKI tended to be older, had lower GCS at admission, and had higher mortality and worse outcomes. However, in a separate study of 171 TBI patients, use of mannitol was identified as an independent risk factor for AKI. Furthermore, elevated doses of mannitol were correlated with higher risks for AKI. While causation cannot be inferred from the study, adequacy of resuscitation should be considered before giving mannitol [57].

15.3.2 Intrinsic Causes of Renal Failure

15.3.2.1 Rhabdomyolysis

Rhabdomyolysis, or the breakdown of striated muscle, is a significant cause of intrinsic renal failure. Rhabdomyolysis in trauma patients usually occurs due to crush injuries, seizure, prolonged immobilization, reperfusion after ischemia, or significant hemorrhage into a muscle compartment [58]. The resulting release of myoglobin into the systemic circulation can cause renal injury due to a direct cytotoxic mechanism, renal vasoconstriction, and renal tubular obstruction [59–62]. Hypovolemia, hyperthermia, electrolyte disturbances, and pre-existing conditions can worsen the clinical syndrome [58]. As measuring myoglobin directly can be more costly, creatine kinase (CK) levels are more often measured. In the largest study of rhabdomyolysis in trauma to date, involving more than 2000 patients, abnormal CK levels were measured in 85% of trauma patients [63]. The most concerning implication, however, is the potential for renal injury. The level of CK associated with an increased renal injury is unclear but has been reported between 500 and 75,000 units/L [63].

In the setting of traumatic rhabdomyolysis, it is important to survey for compartment syndrome. Patients with compartment syndrome require urgent fasciotomy to release compromised muscle groups. Following any required surgical therapy, medical treatment strategies include vigorous hydration to promote renal perfusion and

to dilute myoglobin levels, alkalization of urine to prevent myoglobin deposition within the renal tubule, and mannitol for renal vasodilatation and free-radical scavenging.

The volume of fluid resuscitation in rhabdomyolysis has been advocated as high as 1.5 L NaCl 0.9% per hour during the prehospital phase than 12 L/day hypotonic crystalloid (NaCl 110 mmol/L and bicarbonate 40 mmol/L in glucose 5%) afterwards [33]. This is a large volume, however, and carries the risk of fluid overload and respiratory failure. More contemporary volume goals are 3–6 L in the first 24 h and use of hemodynamic monitoring to guide further resuscitation [33].

Though there are no randomized trials involving the use of mannitol, this osmotic diuretic is thought to protect against rhabdomyolysis-induced AKI by its hydroxyl-free radical scavenger action. Mannitol also increases the volume passing through the renal tubule, potentially preventing myoglobin cast formation [64].

The addition of intravenous bicarbonate to alkalinize the urine is based on laboratory data that at a urine pH >6.5, only 4% of myoglobin aggregates. In comparison, at a pH of less than 5, 70% of myoglobin aggregates. While the theoretical underpinning for bicarbonate is reasonable, its clinical effectiveness remains controversial. A 2004 study stratified 2083 trauma patients into those that had received the combination of bicarbonate and mannitol, and those that did not receive combination therapy. Initiation of the bicarbonate and mannitol combination was determined by physician preference. The combination of bicarbonate and mannitol did not prevent renal failure, dialysis, or mortality [63].

15.3.2.2 Iodinated Contrast Nephropathy

Iodinated contrast materials were developed in the 1920s with the first contrasts highly hyperosmolar, often up to 2200 mOsm/kg. This is much more concentrated than the typical 300 mOsm/kg of normal serum [65]. Used initially to produce intravenous urograms, hyperosmolar contrasts induced fluid shifts from the extravascular space and into the vascular space, potentially predisposing patients to heart failure. These contrast media also induced vasoconstriction in the kidney, potentially decreasing renal perfusion. Contrasts also appeared to have a direct nephrotoxic effect. The use of such hyperosmolar contrasts has declined in favor of less hyperosmolar formulations (780–800 mOsm/kg) and later iso-osmolar formulations. And while contrast formulations are technically improved from their earlier versions, there has been no consensus definition for contrast-induced nephropathy.

There have been no randomized trials involving contrast, and existing studies have been hampered by confounding variables such as sepsis, diabetes, and critical illness. However, a 2009 study involved data from 5.9 million patients with multiple disease processes; patients who had received iodinated contrast were matched to those who had not received iodinated contrast. The risk of AKI in patients receiving and not receiving contrast was identical (5.5% vs. 5.6%, respectively) [66]. In a 2012 study of 571 ICU-admitted trauma patients, use of iodinated contrast was not found to be a risk factor for the development of AKI. [67] More recently, a consensus statement from the American College of Radiology and the National Kidney Foundation concluded that the risk of renal failure following intravenous contrast

administration is lower than previously feared [68]. They suggest, nevertheless, volume expansion with normal saline prior to intravenous contrast administration in patients with an estimated glomerular filtration rate less than 30 mL/min/1.73 m^2. Thus, while iodinated contrast materials still carry the potential of nephrotoxicity, their judicious use in the trauma population appears safe.

15.3.2.3 Other Causes of Nephrotoxicity

In the trauma population, it is also important to consider the presence of nephrotoxic agents. Toxic ingestions can precipitate renal failure. Multiple medications, including antibiotics and nonsteroidal anti-inflammatory drugs, can induce and worsen renal dysfunction [27]. While treatment usually involves removing the nephrotoxic insult and supportive therapy, renal replacement therapy can be considered on an individual basis.

15.3.3 Post-renal (Obstructive) Causes of Renal Failure

Post-renal obstruction represents a minority of the causes of acute kidney injury in the trauma population. Obstruction to the collecting system can occur due to nephrolithiasis or prostatic hypertrophy or direct traumatic injury. Urinary retention due to various causes, as well as urinary catheter obstruction, can produce post-renal failure. Treatment overall involves restoring the pathway for urine clearance.

15.4 Managing Persistent Renal Failure: Volume Management and Renal Replacement Therapy

While we have described a specific approach to acute kidney injury based on underlying etiology, many patients worsen in their renal failure so that diuretic therapy or renal replacement therapy is needed.

Diuresis is usually considered on an individualized basis to improve respiratory status, manage potassium levels, or reduce total body edema. Its use, however, should be judicious and thoughtful. A 2002 study involving 552 ICU patients considered the use of diuretics on the day of and first week after nephrology consultation. The use of diuretics in these critically ill patients with renal failure was associated with mortality and non-recovery of renal function [69]. Though causation could not be inferred, the authors cautioned that the widespread use of diuretics in renal failure should be discouraged. Thus, the most recent KDIGO guidelines recommend against the use of loop diuretics given solely for the prevention of acute kidney injury. The use of diuretics to control fluid overload in diuretic-responsive patients is considered permissible [8].

Persistent renal failure may require renal replacement therapy (RRT). Traditional indications for RRT are recalled by the AEIOU mnemonic: acidosis, electrolyte abnormalities, toxic ingestions, fluid overload, and uremia (Table 15.7) [70].

There has been significant debate between early and late initiation of dialysis. Early dialysis has the theoretical benefit of providing additional support and

Table 15.7 Traditional indications for renal replacement therapy (adapted from Tandukar S, Palevsky PM. Continuous Renal Replacement Therapy: Who, When, Why, and How. Chest. 2019;155(3):626–638. https://doi.org/10.1016/j.chest.2018.09.004)

Traditional indications for renal replacement therapy	
Acidosis	RRT may be initiated for pH less than 7.1–7.2 or serum bicarbonate less than 12–15 mmol/L
Electrolyte abnormalities	RRT is used in a variety of electrolyte abnormalities, but a common threshold is hyperkalemia above 6.5 despite medical management
Ingestions of toxins or drugs	Toxic alcohols, lithium, salicylate, valproic acid, and metformin are dialyzable agents
Overload	While there are no prospective data for specific volume thresholds, RRT is used when volume overload is refractory to diuresis, or when it compromises respiratory or cardiac functions
Uremia	While RRT is indicated for late uremic complications (pericarditis and encephalopathy), it is also used in persistent azotemia prior to the precipitation of overt uremic manifestations

preventing worse organ failure or laboratory deterioration. In contrast, a delayed initiation strategy may prevent the need for dialysis at all. A recent trial of early and late dialysis was published in 2016 and involved 620 patients with KDIGO Stage 3 AKI. The study randomized patients into early dialysis (at time of randomization) vs. late dialysis (by threshold laboratory parameters or if persistent oliguria 72 h after randomization). One hundred fifty-one patients in the late group did not undergo dialysis. There was no difference in 60-day mortality. The delayed dialysis group, however, was noted to have earlier return of diuresis, a marker of renal recovery [71].

While multiple modalities of renal replacement therapy are available, of first consideration is intermittent hemodialysis (IHD). A time efficient modality, IDH is usually accomplished over about 3 h three times a week. In some patients, if required for hemodynamic reasons or solute clearance needs, dialysis times can be extended or dialysis performed more often.

Because of the hemodynamic changes brought on by intermittent dialysis, efforts were made in the 1970s to develop a continuous form of renal replacement therapy (CRRT). In 1977, Peter Kramer performed the first CAVH (continuous arteriovenous hemofiltration) treatment in Gottingen, Germany [72]. Inflow to a filter device was supplied by an arterial cannula and dependent on the patient's own cardiac output. A venous cannula returned blood to the patient. With the development of roller pumps and better double lumen catheters, veno-venous forms of CRRT developed.

Perhaps the simplest form of continuous dialysis is sustained low efficiency dialysis (SLED), which is used to provide fluid clearance without electrolyte modification.

Continuous veno-venous hemofiltration (CVVHF) utilizes a "replacement fluid" with a pre-set electrolyte concentration, which is introduced to the blood flow circuit in either a pre-filter fashion, post-filter fashion, or a combination of the two. In this convective process, hydrostatic pressure pushes solute molecules and fluid out of the filter to deliver fluid and electrolyte clearance of small molecules, such as potassium, urea, and creatinine. A "solvent drag" effect contributes to the partial clearance of some larger molecules, such as myoglobin.

Continuous veno-venous hemodialysis (CVVHD) utilizes a dialysate with a preset electrolyte concentration to flow through the filter in counter-current manner. The resulting concentration gradient clears fluid and electrolytes by diffusion. While CVVHD is more efficient than CVVHF at small molecules (such as potassium, urea, and creatinine), its ability to clear larger molecules is limited.

Continuous veno-venous hemodiafiltration (CVVHDF) is the most complex process and combines CVVHF with CVVHD. It utilizes a replacement fluid to produce solute clearance by convection and a dialysate to promote solute clearance by diffusion.

Overall, however, there have been no firmly demonstrated outcomes benefits from the use of continuous forms of dialysis over IHD. One early comparison of CRRT and IHD showed that CRRT was associated with improved cardiac output, improved blood pressure, and more stable intracranial pressure [73]. Not all studies consistently showed this, however, and a crossover randomized clinical trial involving 27 patients failed to show improvement in hemodynamic parameters [74]. A different randomized trial of 30 septic shock patients found that while CRRT improved hemodynamic parameters, it did not improve makers of perfusion such as gastrointestinal pH values [75].

While hemodynamic improvement is desirable, the true question lies regarding clinical outcomes.

A multicenter, randomized, controlled trial involving 166 patients was conducted comparing IHD and CRRT [76]. Initially, it appeared that continuous therapy was associated with an increase in ICU mortality (59.5% vs. 41.5%, $p < 0.02$) and in-hospital mortality (65.5% vs. 47.6%, $p < 0.02$) relative to intermittent dialysis. On further analysis, despite randomization, it was found that the IHD group had better baseline characteristics, and in particular lower hepatic failure rates, lesser APACHE II and III scores, and a lesser number of failed organ systems. After accounting for the baseline differences in the groups, there was no difference in survival.

Other randomized trials with smaller accrual sizes also did not demonstrate a survival benefit [77, 78]. Thus, while the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for AKI recommends the use of CRRT for patients who are hemodynamically unstable, the strength of this recommendation is low.

By definition of chronic kidney disease, patients who continue to have renal dysfunction after 3 months are characterized as having CKD. Many of these patients require maintenance diuretic therapy. The fraction of trauma patients requiring renal replacement therapy after discharge is uncharacterized. However, in the general ICU population, patients with AKI requiring dialysis have a 50–60% mortality rate; 5–20% remain dialysis dependent at time of discharge [28]. In those receiving CRRT, the intensity of renal replacement therapy does not affect long-term dialysis need [79].

Renal failure in trauma continues to be a significant source of morbidity and mortality. Management begins with addressing volume status, intrinsic renal pathologies, as well as potential urinary outflow issues. Many patients will progress to needing diuresis or renal replacement therapy. A small minority may require ongoing dialysis after discharge (Fig. 15.1). Successfully managing renal insufficiency requires an understanding of the entire spectrum from acute kidney injury to chronic kidney disease.

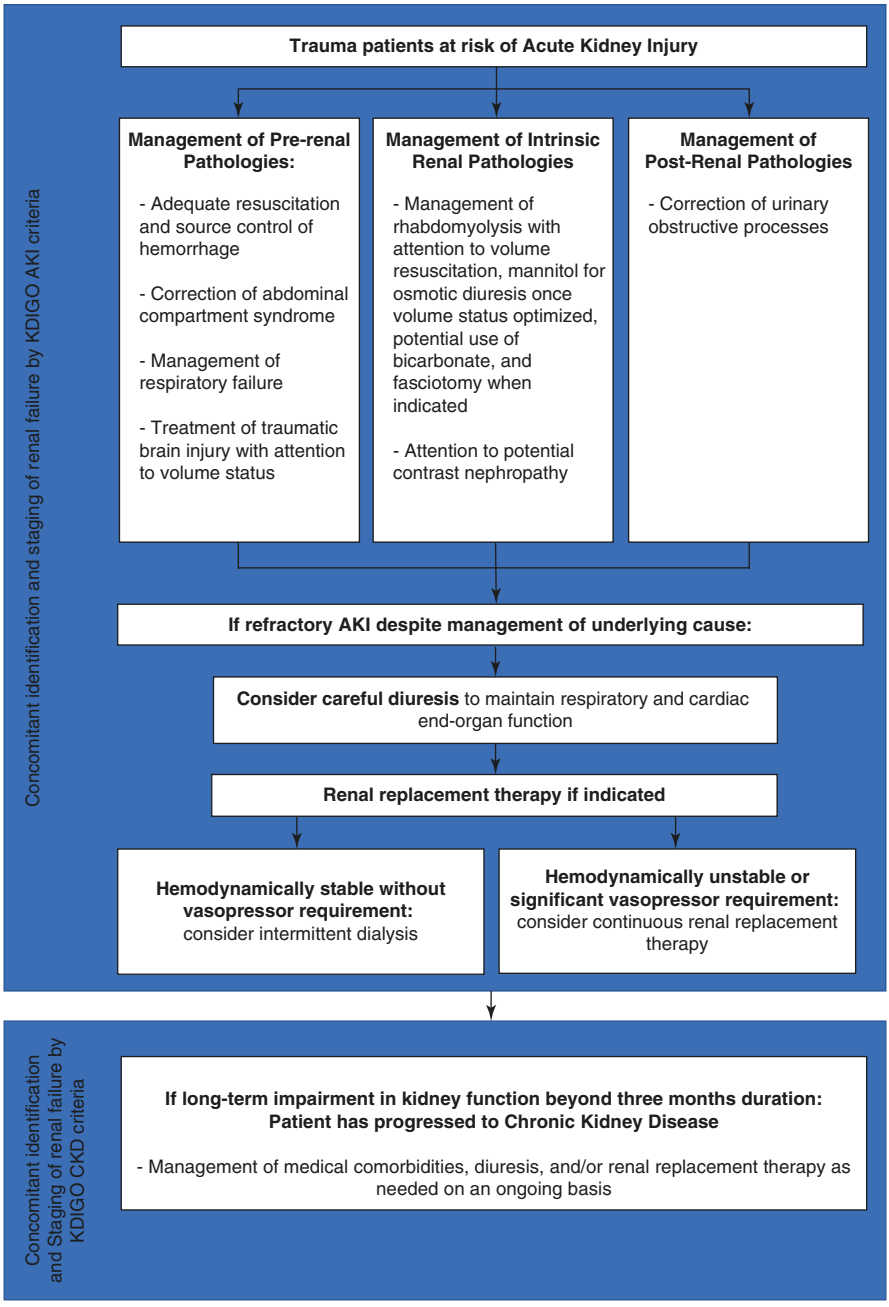


Fig. 15.1 A systematic approach to acute and chronic kidney injury in trauma

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2012;3:1–150.
2. Kellum JA, Levin N, Bouman C, Lameire N. Developing a consensus classification system for acute renal failure. Curr Opin Crit Care. 2002;8(6):509–14.
3. Costantini TW, Fraga G, Fortlage D, Wynn S, Fraga A, Lee J, Doucet J, Bansal V, Coimbra R. Redefining renal dysfunction in trauma: implementation of the Acute Kidney Injury Network staging system. J Trauma. 2009;67(2):283–7. https://doi.org/10.1097/TA.0b013e3181a51a51.
4. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative Workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8(4):R204–12.
5. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, Kellum JA. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care. 2006;10(3):R73.
6. Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. Clin Kidney J. 2013;6(1):8–14. https://doi.org/10.1093/ckj/sfs160.
7. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11(2):R31.
8. Kidney Disease: Improving Global Outcomes (KDIGO) AKI Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2:1–138.
9. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D, Honoré PM, Joannes-Boyau O, Joannidis M, Korhonen AM, Lavrentieva A, Mehta RL, Palevsky P, Roessler E, Ronco C, Uchino S, Vazquez JA, Vidal Andrade E, Webb S, Kellum JA. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411–23. https://doi.org/10.1007/s00134-015-3934-7.
10. Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. Clin Biochem Rev. 2016;37(2):85–98.
11. Morris JA Jr, Mucha P Jr, Ross SE, Moore BF, Hoyt DB, Gentilello L, Landercasper J, Feliciano DV, Shackford SR. Acute posttraumatic renal failure: a multicenter perspective. J Trauma. 1991;31(12):1584–90.
12. Brown CV, Dubose JJ, Hadjizacharia P, Yanar H, Salim A, Inaba K, Rhee P, Chan L, Demetriades D. Natural history and outcomes of renal failure after trauma. J Am Coll Surg. 2008;206(3):426–31. https://doi.org/10.1016/j.jamcollsurg.2007.09.011.
13. Bihorac A, Delano MJ, Schold JD, Lopez MC, Nathens AB, Maier RV, Layon AJ, Baker HV, Moldawer LL. Incidence, clinical predictors, genomics, and outcome of acute kidney injury among trauma patients. Ann Surg. 2010;252(1):158–65. https://doi.org/10.1097/SLA.0b013e3181deb6bc.
14. Søvik S, Isachsen MS, Nordhuus KM, Tveiten CK, Eken T, Sunde K, Brurberg KG, Beitland S. Acute kidney injury in trauma patients admitted to the ICU: a systematic review and meta-analysis. Intensive Care Med. 2019;45(4):407–19. https://doi.org/10.1007/s00134-019-05535-y.
15. Gomes E, Antunes R, Dias C, Araújo R, Costa-Pereira A. Acute kidney injury in severe trauma assessed by RIFLE criteria: a common feature without implications on mortality? Scand J Trauma Resusc Emerg Med. 2010;18:1. https://doi.org/10.1186/1757-7241-18-1.
16. Stewart IJ, Sosnov JA, Howard JT, Chung KK. Acute kidney injury in critically injured combat veterans: a retrospective cohort study. Am J Kidney Dis. 2016;68(4):564–70. https://doi.org/10.1053/j.ajkd.2016.03.419.

17. Heegard KD, Stewart IJ, Cap AP, Sosnov JA, Kwan HK, Glass KR, Morrow BD, Latack W, Henderson AT, Saenz KK, Siew ED, Ikizler TA, Chung KK. Early acute kidney injury in military casualties. J Trauma Acute Care Surg. 2015;78(5):988–93. https://doi.org/10.1097/TA.0000000000000607.
18. Lai WH, Rau CS, Wu SC, Chen YC, Kuo PJ, Hsu SY, Hsieh CH, Hsieh HY. Post-traumatic acute kidney injury: a cross-sectional study of trauma patients. Scand J Trauma Resusc Emerg Med. 2016;24(1):136.
19. Reilly JP, Anderson BJ, Mangalmurti NS, Nguyen TD, Holena DN, Wu Q, Nguyen ET, Reilly MP, Lanken PN, Christie JD, Meyer NJ, Shashaty MG. The ABO Histo-blood group and AKI in critically ill patients with trauma or sepsis. Clin J Am Soc Nephrol. 2015;10(11):1911–20. https://doi.org/10.2215/CJN.12201214.
20. Shashaty MG, Meyer NJ, Localio AR, Gallop R, Bellamy SL, Holena DN, Lanken PN, Kaplan S, Yarar D, Kawut SM, Feldman HI, Christie JD. African American race, obesity, and blood product transfusion are risk factors for acute kidney injury in critically ill trauma patients. J Crit Care. 2012;27(5):496–504. https://doi.org/10.1016/j.jcrc.2012.02.002.
21. Fujinaga J, Kuriyama A, Shimada N. Incidence and risk factors of acute kidney injury in the Japanese trauma population: a prospective cohort study. Injury. 2017;48(10):2145–9. https://doi.org/10.1016/j.injury.2017.08.022.
22. Eriksson M, Brattström O, Mårtensson J, Larsson E, Oldner A. Acute kidney injury following severe trauma: risk factors and long-term outcome. J Trauma Acute Care Surg. 2015;79(3):407–12. https://doi.org/10.1097/TA.0000000000000727.
23. Wohlauer MV, Sauaia A, Moore EE, Burlew CC, Banerjee A, Johnson J. Acute kidney injury and posttrauma multiple organ failure: the canary in the coal mine. J Trauma Acute Care Surg. 2012;72(2):373–8. https://doi.org/10.1097/TA.0b013e318244869b; discussion 379–80.
24. Acharya V, Olivero J. The KIDNEY as an endocrine organ. Method Debakey Cardiovasc J. 2018;14(4):305–7. https://doi.org/10.14797/mdcj-14-4-305.
25. Li X, Hassoun HT, Santora R, Rabb H. Organ crosstalk: the role of the kidney. Curr Opin Crit Care. 2009;15(6):481–7. https://doi.org/10.1097/MCC.0b013e328332f69e. Erratum in: Curr Opin Crit Care. 2010 Apr;16(2)180. PMID: 19851101.
26. Lee SA, Cozzi M, Bush EL, Rabb H. Distant organ dysfunction in acute kidney injury: a review. Am J Kidney Dis. 2018;72(6):846–56. https://doi.org/10.1053/j.ajkd.2018.03.028.
27. Eachempati SR, Wang JC, Hydo LJ, Shou J, Barie PS. Acute renal failure in critically ill surgical patients: persistent lethality despite new modes of renal replacement therapy. J Trauma. 2007;63(5):987–93.
28. Hoste EA, Schurgers M. Epidemiology of acute kidney injury: how big is the problem? Crit Care Med. 2008;36(4 Suppl):S146–51. https://doi.org/10.1097/CCM.0b013e318168c590.
29. Ala-Kokko T, Ohtonen P, Laurila J, Martikainen M, Kaukoranta P. Development of renal failure during the initial 24 h of intensive care unit stay correlates with hospital mortality in trauma patients. Acta Anaesthesiol Scand. 2006;50(7):828–32.
30. Bagshaw SM, George C, Gibney RT, Bellomo R. A multi-center evaluation of early acute kidney injury in critically ill trauma patients. Ren Fail. 2008;30(6):581–9. https://doi.org/10.1080/08860220802134649.
31. Podoll AS, Kozar R, Holcomb JB, Finkel KW. Incidence and outcome of early acute kidney injury in critically-ill trauma patients. PLoS One. 2013;8(10):e77376. https://doi.org/10.1371/journal.pone.0077376.
32. Ricksten S, Bragadottir G, Redfors B. Renal oxygenation in clinical acute kidney injury. Crit Care. 2013;17(2):221. https://doi.org/10.1186/cc12530.
33. Harrois A, Libert N, Duranteau J. Acute kidney injury in trauma patients. Curr Opin Crit Care. 2017;23(6):447–56. https://doi.org/10.1097/MCC.0000000000000463.
34. Blalock A. Principles of surgical care: shock and other problems. St. Louis, MO: C.V. Mosby; 1940.
35. Guly UM, Turney JH. Post-traumatic acute renal failure, 1956-1988. Clin Nephrol. 1990;34(2):79–83.

36. 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. J Trauma. 1995;38(1):70–8.
37. Bulger EM, May S, Kerby JD, Emerson S, Stiell IG, Schreiber MA, Brasel KJ, Tisherman SA, Coimbra R, Rizoli S, Minei JP, Hata JS, Sopko G, Evans DC, Hoyt DB, ROC investigators. Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: a randomized, placebo controlled trial. Ann Surg. 2011;253(3):431–41. https://doi.org/10.1097/SLA.0b013e3181fcdb22.
38. Ho KM, Leonard AD. Lack of effect of unrefrigerated young whole blood transfusion on patient outcomes after massive transfusion in a civilian setting. Transfusion. 2011;51(8):1669–75. https://doi.org/10.1111/j.1537-2995.2010.02975.x.
39. Spinella PC, Perkins JG, Grathwohl KW, Beekley AC, Holcomb JB. Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. J Trauma. 2009;66(4 Suppl):S69–76. https://doi.org/10.1097/TA.0b013e31819d85fb.
40. Perkins JG, Cap AP, Spinella PC, Shorr AF, Beekley AC, Grathwohl KW, Rentas FJ, Wade CE, Holcomb JB. 31st Combat Support Hospital Research Group. Comparison of platelet transfusion as fresh whole blood versus apheresis platelets for massively transfused combat trauma patients. Transfusion. 2011;51(2):242–52. https://doi.org/10.1111/j.1537-2995.2010.02818.x.
41. Cotton BA, Podbielski J, Camp E, Welch T, del Junco D, Bai Y, Hobbs R, Scroggins J, Hartwell B, Kozar RA, Wade CE, Holcomb JB. Early Whole Blood Investigators. A randomized controlled pilot trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. Ann Surg. 2013;258(4):527–32. https://doi.org/10.1097/SLA.0b013e3182a4ffa0.
42. Shoemaker WC, Appel P, Bland R. Use of physiologic monitoring to predict outcome and to assist in clinical decisions in critically ill postoperative patients. Am J Surg. 1983;146(1):43–50.
43. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M. Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368–77.
44. ARISE Investigators; ANZICS Clinical Trials Group, Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ, Higgins AM, Holdgate A, Howe BD, Webb SA, Williams P. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371(16):1496–506. https://doi.org/10.1056/NEJMoa1404380.
45. ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F, Filbin MR, Shapiro NI, Angus DC. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370(18):1683–93. https://doi.org/10.1056/NEJMoa1401602.
46. Mouncey PR, Osborn TM, Power GS, Harrison DA, Sadique MZ, Grieve RD, Jahan R, Harvey SE, Bell D, Bion JF, Coats TJ, Singer M, Young JD, Rowan KM. ProMISe Trial Investigators. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372(14):1301–11. https://doi.org/10.1056/NEJMoa1500896.
47. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45(3):486–552. https://doi.org/10.1097/CCM.0000000000002255.
48. Holodinsky JK, Roberts DJ, Ball CG, Blaser AR, Starkopf J, Zygun DA, Stelfox HT, Malbrain ML, Jaeschke RC, Kirkpatrick AW. Risk factors for intra-abdominal hypertension

and abdominal compartment syndrome among adult intensive care unit patients: a systematic review and meta-analysis. Crit Care. 2013;17(5):R249. https://doi.org/10.1186/cc13075.
49. Balogh Z, McKinley BA, Cocanour CS, Kozar RA, Valdivia A, Sailors RM, Moore FA. Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome. Arch Surg. 2003;138(6):637–42.
50. Harman PK, Kron IL, McLachlan HD, Freedlender AE, Nolan SP. Elevated intra-abdominal pressure and renal function. Ann Surg. 1982;196(5):594–7.
51. Doty JM, Saggi BH, Blocher CR, Fakhry I, Gehr T, Sica D, Sugerman HJ. Effects of increased renal parenchymal pressure on renal function. J Trauma. 2000;48(5):874–7.
52. Doty JM, Saggi BH, Sugerman HJ, Blocher CR, Pin R, Fakhry I, Gehr TW, Sica DA. Effect of increased renal venous pressure on renal function. J Trauma. 1999;47(6):1000–3.
53. Deeren DH, Dits H, Malbrain ML. Correlation between intra-abdominal and intracranial pressure in nontraumatic brain injury. Intensive Care Med. 2005;31(11):1577–81.
54. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, Duchesne J, Bjorck M, Leppaniemi A, Ejike JC, Sugrue M, Cheatham M, Ivatury R, Ball CG, Reintam Blaser A, Regli A, Balogh ZJ, D'Amours S, Debergh D, Kaplan M, Kimball E, Olvera C, Pediatric Guidelines Sub-Committee for the World Society of the Abdominal Compartment Syndrome. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 2013;39(7):1190–206. https://doi.org/10.1007/s00134-013-2906-z.
55. Kuiper JW, Groeneveld AB, Slutsky AS, Plötz FB. Mechanical ventilation and acute renal failure. Crit Care Med. 2005;33(6):1408–15.
56. Li N, Zhao WG, Zhang WF. Acute kidney injury in patients with severe traumatic brain injury: implementation of the acute kidney injury network stage system. Neurocrit Care. 2011;14(3):377–81. https://doi.org/10.1007/s12028-011-9511-1.
57. Fang L, You H, Chen B, Xu Z, Gao L, Liu J, Xie Q, Zhou Y, Gu Y, Lin S, Ding F. Mannitol is an independent risk factor of acute kidney injury after cerebral trauma: a case-control study. Ren Fail. 2010;32(6):673–9. https://doi.org/10.3109/0886022X.2010.486492.
58. Polderman KH. Acute renal failure and rhabdomyolysis. Int J Artif Organs. 2004;27(12):1030–3.
59. Slater MS, Mullins RJ. Rhabdomyolysis and myoglobinuric renal failure in trauma and surgical patients: a review. J Am Coll Surg. 1998;186(6):693–716.
60. Zager RA. Rhabdomyolysis and myohemoglobinuric acute renal failure. Kidney Int. 1996;49(2):314–26.
61. Better OS, Stein JH. Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. N Engl J Med. 1990;322(12):825–9.
62. Odeh M. The role of reperfusion-induced injury in the pathogenesis of the crush syndrome. N Engl J Med. 1991;324(20):1417–22.
63. Brown CV, Rhee P, Chan L, Evans K, Demetriades D, Velmahos GC. Preventing renal failure in patients with rhabdomyolysis: do bicarbonate and mannitol make a difference? J Trauma. 2004;56(6):1191–6.
64. Zager RA. Combined mannitol and deferoxamine therapy for myohemoglobinuric renal injury and oxidant tubular stress. Mechanistic and therapeutic implications. J Clin Invest. 1992;90(3):711–9.
65. Do C. Intravenous contrast: friend or foe? a review on contrast-induced nephropathy. Adv Chronic Kidney Dis. 2017;24(3):147–9. https://doi.org/10.1053/j.ackd.2017.03.003.
66. Wilhelm-Leen E, Montez-Rath ME, Chertow G. Estimating the risk of radiocontrast-associated nephropathy. J Am Soc Nephrol. 2017;28(2):653–9. https://doi.org/10.1681/ASN.2016010021.
67. Kim DY, Kobayashi L, Costantini TW, Chang D, Fortlage D, Curry T, Wynn S, Doucet J, Bansal V, Coimbra R. Is contrast exposure safe among the highest risk trauma patients? J Trauma Acute Care Surg. 2012;72(1):61–6. https://doi.org/10.1097/TA.0b013e31823f36e0.
68. Davenport MS, Perazella MA, Yee J, Dillman JR, Fine D, McDonald RJ, Rodby RA, Wang CL, Weinreb JC. Use of intravenous iodinated contrast media in patients with kidney disease:

consensus statements from the American College of Radiology and the National Kidney Foundation. Radiology. 2020;294(3):660–8. https://doi.org/10.1148/radiol.2019192094.
69. Mehta RL, Pascual MT, Soroko S, Chertow GM, PICARD Study Group. Diuretics, mortality, and nonrecovery of renal function in acute renal failure. JAMA. 2002;288(20):2547–53.
70. Tandukar S, Palevsky PM. Continuous renal replacement therapy: who, when, why, and how. Chest. 2019;155(3):626–38. https://doi.org/10.1016/j.chest.2018.09.004.
71. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, Boyer A, Chevrel G, Lerolle N, Carpentier D, de Prost N, Lautrette A, Bretagnol A, Mayaux J, Nseir S, Megarbane B, Thirion M, Forel JM, Maizel J, Yonis H, Markowicz P, Thiery G, Tubach F, Ricard JD, Dreyfuss D, AKIKI Study Group. Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med. 2016;375(2):122–33. https://doi.org/10.1056/NEJMoa1603017.
72. Ronco C. Continuous renal replacement therapy: forty-year anniversary. Int J Artif Organs. 2017;40:257. https://doi.org/10.5301/ijao.5000610.
73. Davenport A, Will EJ, Davison AM. Effect of renal replacement therapy on patients with combined acute renal and fulminant hepatic failure. Kidney Int Suppl. 1993;41:S245–51.
74. Misset B, Timsit JF, Chevret S, Renaud B, Tamion F, Carlet J. A randomized cross-over comparison of the hemodynamic response to intermittent hemodialysis and continuous hemofiltration in ICU patients with acute renal failure. Intensive Care Med. 1996;22(8):742–6.
75. John S, Griesbach D, Baumgärtel M, Weihprecht H, Schmieder RE, Geiger H. Effects of continuous haemofiltration vs intermittent haemodialysis on systemic haemodynamics and splanchnic regional perfusion in septic shock patients: a prospective, randomized clinical trial. Nephrol Dial Transplant. 2001;16(2):320–7.
76. Mehta RL, McDonald B, Gabbai FB, Pahl M, Pascual MT, Farkas A, Kaplan RM. Collaborative Group for Treatment of ARF in the ICU. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. Kidney Int. 2001;60(3):1154–63.
77. Augustine JJ, Sandy D, Seifert TH, Paganini EP. A randomized controlled trial comparing intermittent with continuous dialysis in patients with ARF. Am J Kidney Dis. 2004;44(6):1000–7.
78. Uehlinger DE, Jakob SM, Ferrari P, Eichelberger M, Huynh-Do U, Marti HP, Mohaupt MG, Vogt B, Rothen HU, Regli B, Takala J, Frey FJ. Comparison of continuous and intermittent renal replacement therapy for acute renal failure. Nephrol Dial Transplant. 2005;20(8):1630–7.
79. Gallagher M, Cass A, Bellomo R, Finfer S, Gattas D, Lee J, Lo S, McGuinness S, Myburgh J, Parke R, Rajbhandari D. POST-RENAL Study Investigators and the ANZICS Clinical Trials Group. Long-term survival and dialysis dependency following acute kidney injury in intensive care: extended follow-up of a randomized controlled trial. PLoS Med. 2014;11(2):e1001601. https://doi.org/10.1371/journal.pmed.1001601.

Post-injury Bone Marrow Failure

16

Gabrielle D. Briggs

16.1 Bone Marrow as an Organ

16.1.1 Bone Marrow Architecture and Function

Bone marrow is found in the bony matrix of trabecular bone within long and axial bones and is an essential organ for the storage and maturation of haematopoietic cells, which give rise to all cells of the blood and immune system. In addition to haematopoietic progenitors, bone marrow contains stromal, non-haematopoietic cells that are not only involved in the maintenance of bone and marrow tissue, but are essential for the growth, differentiation and migration of haematopoietic progenitors through their expression of growth factors, adhesion molecules and chemokines. The cellular architecture within the bone marrow is highly organized and heterogeneous, with the progenitor cells positioned in niches around the capillary structure and stromal cells according to the level of maturation. These "haematopoietic niches" allow specialized differentiation to occur; however, it should be noted that the cell types and factors involved in different haematopoietic niches are still areas of active discovery and what is presented here represents our current understanding.

The vasculature of the bone marrow consists of sinusoidal capillaries concentrated close to the endosteum, comprising a discontinuous single endothelial layer capillary networks with a central draining sinus which form the sites of bone marrow cell egress into the circulation, as well as free movement of plasma proteins and molecules into the bone marrow tissue [1]. Endosteal bone surfaces contain osteoblasts (bone forming cells) and osteoclasts (bone absorbing cells) [2]. Adipocytes, which make up 70% of bone marrow volume in adults are distributed throughout the bone marrow and act as an energy source with additional endocrine roles and

G. D. Briggs (✉)
School of Medicine and Public Health, University of Newcastle, Callaghan, NSW, Australia
e-mail: gabrielle.briggs@newcastle.edu.au

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_16

secretion of factors that can regulate haematopoiesis [3]. Mesenchymal stem cells (MSCs) give rise to osteoblasts and adipocytes but have also been shown to play a direct role in promoting haematopoiesis by localizing to sinusoids [2]. Similarly, endothelial cells of the sinusoids also support haematopoiesis beyond direct contact through secretion of paracrine factors [4]. Macrophages perform essential roles in supporting and regulating haematopoiesis, particularly erythropoiesis [5]. Bone marrow function is also controlled by autonomic inputs, which contact both bone marrow blood vessels and bone marrow cells [6], particularly the stromal cells [7], as a way of indirectly modulating haematopoiesis.

16.1.1.1 Haematopoiesis

Haematopoiesis refers to the expansion of haematopoietic progenitor cells and maturation into mature blood cells. Haematopoiesis begins with pluripotent haematopoietic stem cells (HSCs) that are associated with the endosteum (endosteal niche), ensuring that they remain in the bone marrow, or to a greater extent, with haematopoietic niches adjacent to sinusoids (perivascular niche) that are fostered by specialized MSCs [8]. Endosteal HSCs are relatively quiescent and are thought to be the long-term reservoir of HSCs, while perivascular HSCs have higher proliferative activity and are thus thought to meet haematopoietic demands over the short term or be available for release into the circulation in their undifferentiated form [9]. The first stage of haematopoiesis results in the differentiation of HSCs into multipotent progenitors that expand and differentiate into either common myeloid or lymphoid progenitors, which actively proliferate and give rise to cells of the myeloid lineage (erythrocytes, megakaryocytes, monocytes, macrophages, dendritic cells, neutrophils, eosinophils, basophils and mast cells) and lymphoid lineage (B and T lymphocytes and natural killer cells) [10]. Active haematopoietic bone marrow is known as red bone marrow, existing in all bones at birth. Over time, this is replaced by yellow bone marrow (mainly in the extremities) [11], where MSC-derived adipocytes accumulate and where the bone marrow no longer supports haematopoiesis [3]. However, this process is reversible and dynamic in times of increased demand [12]. Overall, the process of steady-state haematopoiesis is under a mixture of transcriptional and environmental control according to the niche microenvironment, but in times of acute changes to circulating blood cells, or requirements for increased turnover, humoral and neuroendocrine control can accelerate, regulate and skew the cellular output from the bone marrow by promoting the maturation of committed progenitors, referred to as emergency haematopoiesis [13]. Haematopoiesis also occurs outside the bone marrow (e.g. spleen, thymus); however, this will not be discussed in this chapter.

16.1.1.2 Erythropoiesis

The process of erythrocyte maturation, erythropoiesis, begins with common myeloid progenitors differentiating into committed megakaryocyte-erythroid progenitors, which undergo a series of differentiation steps to form erythrocyte progenitor cells (BFU-E and CFU-E) according to factors such as glucocorticoids and SCF for BFU-E expansion and erythropoietin (EPO) for CFU-E expansion [14]. CFU-E

cells differentiate into pro-erythroblasts that begin to condense chromatin, reduce cell size, express the transferrin receptor for iron acquisition, synthesize haemoglobin and associate into specialized units called erythroblastic islands that are distributed throughout the bone marrow. Erythroblastic islands consist of a central macrophage encircled by a crown of up to 5–30 erythroblasts that are cradled by dendritic processes [15]. As erythroblasts mature, this unit moves along the ECM towards the sinusoids [16], the central macrophage providing growth factors and iron for erythrocyte progenitors (although the form of iron is currently unknown) [17]. Upon the maturation into reticulocytes, nuclei and mitochondria are extruded and phagocytosed by the central macrophage [18]. Reticulocytes then contact sinusoids and enter the circulation, where they undergo the final stages of cytoskeletal remodelling to develop the classical biconcave morphology of the mature erythrocyte [19]. From HSC to mature erythrocyte, erythropoiesis takes approximately 14 days in humans, resulting in an output of 2.5 million erythrocytes per second amounting to 220 billion erythrocytes per day [20].

A major regulator of erythropoiesis is EPO, which under hypoxic conditions is produced by the kidney and transported from the circulation into the bone marrow, where it stimulates erythropoiesis, especially at the CFU-stage, increasing the numbers of cells surviving to maturity [21].

16.1.1.3 Megakaryopoiesis

Megakaryopoiesis, the process by which platelet-producing megakaryocytes are formed, also begins with common myeloid progenitor-derived megakaryocyte-erythroid progenitor cells; however, the maturation pathway is not as well understood as erythropoiesis. Megakaryocytes can also be generated directly from long-term HSCs [22]. Megakaryoblasts reside in the endosteal niche [23] and are driven to proliferate via the actions of osteoblast-derived thrombopoietin (TPO) [24] and mature and migrate towards sinusoids via stromal-derived chemokines and growth factors [25]. Prior to being fully mature, megakaryocytes undergo a process called endomitosis, where the genome and other cytoplasmic components are replicated up to 64 times, producing a large (~150 μm) cell [26]. Mature megakaryocytes then interact with the sinusoids, extruding long processes called proplatelets into the vascular lumen, which directly release platelets into the circulation [27] and resulting in the turnover of 100 billion platelets per day [28]. More recently it has been shown that megakaryocytes also migrate to the lungs to produce platelets [29].

16.1.1.4 Myelopoiesis

Myelopoiesis refers to the maturation of cells that ultimately become granulocytes, monocytes, macrophages and dendritic cells. Granulopoiesis, the process by which neutrophils, basophils, eosinophils and mast cells are formed, begins with common myeloid progenitors differentiating into granulocyte–monocyte progenitors. Expansion of this pool is promoted by granulocyte-macrophage colony stimulating factor (GM-CSF) [30]. Differentiation into myeloblasts is the first step of committed granulopoiesis, driven by circulating granulocyte colony stimulating factor (G-CSF) [31] where cells will form increasing numbers of granules and undergo

distinctive changes in nuclear morphology. At this point of differentiation, levels of different cytokines govern the maturation into neutrophils, eosinophils, basophils and mast cells, with neutrophils being the predominant endpoint, taking 12 days to complete maturation [32]. A large number of mature neutrophils remain associated at sinusoids for 4–6 days [33], available for rapid release during the inflammatory response. Under non-disease states, granulopoiesis produces approximately 0.5–1 million cells per second, amounting to 50–100 billion cells per day [34].

Monoblasts develop from the granulocyte-monocyte progenitors and mature into monocytes over 6 days [35]; however, a large storage pool of immature monocytes exist in the bone marrow, which can undergo the final stages of maturation in 2 days [36]. Unlike neutrophils, monocytes are released into the bloodstream upon maturation without any mature bone marrow reservoir, after which they spend 1–3 days in the circulation [36] and migrate into tissues where they can further proliferate and differentiate into macrophages and dendritic cells.

16.1.1.5 Lymphopoiesis

Common lymphoid progenitor cells differentiate into either B-cell progenitors or progenitors of T-cells and natural killer cells. B-cell maturation includes rearrangement of the Ig heavy chain variable region [37] and occurs under the influence of local stromal factors which also localize maturing B-cells to define niches according to their maturation level [38]. Immature B-cells that express the B-cell receptor then localize to sinusoids; however, they remain attached to the vascular lumen [39], forming a transient vascular bone marrow niche prior to migrating to secondary lymphoid tissues. Additionally, mature plasma B-cells can be found in the bone marrow [40]. T-cell progenitors leave the bone marrow early in their maturation, with the remainder of their maturation occurring in the thymus, after which they enter the circulation as fully mature T-cells [41]. The development of natural killer cells is poorly understood; however, early development is known to occur in the bone marrow, driven by IL-15 [42], with immature natural killer cells moving to secondary lymphoid tissues to develop further [41].

16.2 The Response of Bone Marrow to Injury and Shock

16.2.1 Clinical Signs

Critically ill trauma patients typically demonstrate an immediate and sustained systemic inflammatory response which in some evolves over the following weeks into an immunosuppressed state with sustained inflammation and catabolism, resulting in recurrent nosocomial infections, referred to as critical care illness syndrome and PICS (persistent inflammation immunosuppression and catabolism syndrome) [43], which is likely brought about (at least in part) by bone marrow failure.

The most overt sign of post-injury bone marrow failure is anaemia [44], and consequently most bone marrow failure research is focused on this compartment. Traumatic injury and haemorrhagic shock result in massive and immediate loss of

red blood cells and despite multiple transfusions, severely injured patients fail to maintain adequate red blood cell counts and develop persistent anaemia that is not fully explained by blood loss [44] which can last beyond discharge from hospital [45]. Traumatic injury causes a sharp increase in the number of circulating neutrophils [46] and the appearance of circulating immature neutrophils, which are initially greater in number in those who subsequently develop MOF/PICS [47] and remain elevated [48]. For lymphocytes, traumatic injury produces an immediate increase in circulating natural killer cells, which is associated with lymphopenia at 48 h and subsequent MOF [49]. While severe injury and shock cause initial loss and consumption of platelets, critically ill trauma patients typically display transient reactive thrombocytosis after approximately 1 week. Patients with multiple organ failure have a delayed thrombocytosis compared to those without MOF; however, paradoxically, post-injury thrombocytosis is associated with survival rather than death [50].

16.2.2 Mechanisms

Following traumatic injury and haemorrhagic shock, high numbers of haematopoietic progenitors have been measured in the circulation in the weeks following injury [51]. Animal models demonstrate that these circulating progenitors migrate to sites of injury and are essential to tissue repair processes [52]; however, in both animals and humans, movement of bone marrow progenitors into the circulation is associated with a concomitant loss of bone marrow cellularity [44]. Specifically, there are reduced numbers of erythroid progenitors in the bone marrow following injury and a progressive shift towards myelopoiesis and away from erythropoiesis over the following week [44, 53], consistent with the clinical signs of persistent anaemia and neutrophilia. In terms of the mechanism, animal studies have shown that post-injury release of haematopoietic progenitors from bone marrow is mediated by activation of sympathetic efferents in the bone marrow. After injury, noradrenaline released from sympathetic terminals activates bone marrow macrophages to release the damage-associated molecular pattern, HMGB-1, which in turn causes G-CSF release [54]. G-CSF downregulates expression of stromal adhesion molecules, thus mobilizing HCS and allowing egress into the circulation [55]. G-CSF also directly drives the proliferation of neutrophil progenitors, which may further drive common myeloid progenitors towards myelopoiesis, restricting the generation of erythroid progenitors.

In addition to the actions of noradrenaline from sympathetic terminals in the bone marrow, traumatic injury and haemorrhagic shock induce high concentrations of circulating catecholamines that can be sustained for at least a week. While physiological concentrations of catecholamines promote haematopoiesis, elevated noradrenaline directly and potently inhibits proliferation of erythroid progenitors in ex vivo studies [56] and animal models [57] but has no inhibitory effect on common myeloid progenitors [56], providing another mechanism for the post-injury shift towards myelopoiesis. Elderly trauma patients have been shown to have 4 times the

amount of circulating noradrenaline [58] than younger counterparts, which could contribute to the higher incidence and severity of post-injury anaemia in elderly trauma patients [59].

Hypoxic conditions following traumatic injury stimulate increases in EPO, which is markedly elevated in trauma patient plasma [44, 53, 60]. Under normal conditions, EPO should stimulate erythroid progenitor growth; however, this is not the case in trauma patients. Studies of EPO in the bone marrow indicate that despite the high plasma concentration, EPO in the bone marrow of trauma patients remains low [53] and the mechanism for this is currently unknown. In addition, EPO receptor expression is downregulated in the bone marrow post-injury [53] most likely due to the loss of EPO receptor-expressing erythroid progenitors.

Anaemia of inflammation refers to a global response to infectious threats, whereby hepcidin, the master regulator of iron absorption, is increased in response to IL-6 and as a result, iron absorption, transferrin saturation and transferrin protein levels are markedly reduced to prevent microbes' scavenging of host iron. Post-injury inflammation produces the same response [61]. Studies of iron regulation in post-injury bone marrow indicate that transferrin and ferroportin are increased [53], but transferrin receptors decreased. Again, this could be due to low numbers of transferrin receptor-expressing erythroid progenitors in post-injury bone marrow.

The post-injury inflammatory response causes neutrophil margination and infiltration into the tissues. Given their short half-life, circulating neutrophils need to be replaced from the bone marrow stores in the hours to days following injury, thus driving emergency myelopoiesis. Both bone marrow and plasma G-CSF are elevated after traumatic injury [53], which stimulate expansion of neutrophil progenitors. Over the longer term for ICU-admitted trauma patients, neutrophilia is maintained; however, it has been shown that the function of neutrophils is impaired [62].

Post-injury bone marrow has been shown to accumulate immunosuppressive types of myeloid cells named myeloid-derived suppressor cells (MDSCs), which are also found in cancer, sepsis, traumatic brain injury and burns [62]. MDSCs can be either granulocytic or monocytic; the former cannot differentiate into mature neutrophils, while monocytic MDSCs retain the ability to mature under certain conditions [62]. MDSCs are immunosuppressive through their ability to suppress T-cell function [63]. As well as their appearance in high numbers in the bone marrow, granulocytic MDSCs are present in the circulation within 24 h of injury and remain detectable for weeks, while monocytic MDSCs appear at later timepoints [62]. MDSCs have been shown to be present at injury sites [62], with their assumed role being to limit inflammation and T-cell responses, although this is still an active area of investigation.

16.3 Prediction and Diagnosis of Bone Marrow Failure

While bone marrow failure is a well-known feature of critially ill truma patients, this is not caputured in the current MOF scales due to the lack of a consensus definition and diagnostic tools. The above evidence suggests certain cell types

and circulating biomarkers that could be used to monitor the bone marrow in critically ill trauma patients (beyond circulating blood cell counts). Plasma G-CSF has been shown to correlate strongly with subsequent anaemia in trauma patients [51] and not with age, gender of injury severity, potentially making it a suitable biomarker. Given that a hypercatecholamine state leads to increases in G-CSF, mobilization of haematopoietic progenitors and reduced erythropoiesis, endogenous circulating noradrenaline is another candidate biomarker for bone marrow status, however, given that critically ill trauma patients may receive noradrenaline for shock management, this may confound its diagnostic utility. Given that MDSCs are present in the circulation and represent dysfunctional myelopoiesis, the number of circulating MDSCs may also allow the severity of bone marrow dysfunction to be assessed; however, characterization of MDSCs is not currently routine. Elevated hepcidin also has the potential to reflect the extent and duration of anaemia [61]. Hepcidin is known to increase after blood transfusions due to the free iron, so correcting for recent transfusions may be required.

16.4 Therapeutic Options for Post-injury Bone Marrow Failure

With anaemia being the most overt manifestation of post-injury bone marrow failure, therapies targeted to the erythroid compartment and maintenance of red cell counts/haemoglobin levels are the standard of care, including packed red cell transfusions. Given that the most drastic changes to bone marrow function occur shortly after injury, the possibility remains that early preventative therapies aimed at protecting the bone marrow could be successful.

16.4.1 EPO Therapy

Recombinant human EPO (epoetin alfa) has been trialled in critically ill patients with the aim of stimulating erythroid progenitor growth and maturation. Weekly EPO for up to 3 weeks did not decrease transfusion requirements, but did lead to an increased haemoglobin at Day 29, and in a subgroup analysis, trauma patient mortality at Day 29 was significantly reduced [64]. The authors postulate that since transfusions were not decreased by EPO, the reduction in mortality was due to non-haematopoietic, antiapoptotic effects of EPO. However, another possibility is the reduction in myelopoiesis that could result from driving erythropoiesis under conditions of limiting upstream progenitors, thus limiting the negative effects of neutrophil activation and MDSC expansion. However, this study did not examine any myeloid-related variables. In another study, recombinant EPO was found to produce no change in long-term functional outcomes of critically ill trauma patients [65]. Clinical trials of EPO in trauma patients are ongoing to better understand the specific benefits in post-injury anaemia.

16.4.2 Targeting Iron Dysfunction

While iron dysregulation is clearly a contributing factor to persistent anaemia following injury, a clinical trial of iron supplementation found no effect on alleviating anaemia or reducing transfusion requirements [66], possibly due to the myriad of other factors preventing the generation of erythroid progenitors that would utilize the iron.

Inhibition of hepcidin synthesis is a promising therapeutic option, with phase I and II clinical trials demonstrating the ability to alleviate anaemia in critically ill patients, including the use of high dose vitamin D [67]. This approach would not be without its risks in the critically ill trauma population. Given that the anaemia of inflammation evolved to limit the growth of bacterial pathogens, increasing iron availability through hepcidin inhibition may increase infection rates in this already immunosuppressed cohort, and infection rates would be an important variable to include in any study of hepcidin inhibition.

16.4.3 Sympathetic Activation

Strong evidence from animal models of trauma and haemorrhagic shock indicate that blockade of sympathetic activation of the bone marrow via beta-adrenergic antagonist, propranolol, decreases G-CSF levels, reduces haematopoietic progenitor release and alleviates post-injury anaemia [68, 69]. However, use of propranolol in a clinical trial of trauma patients did not reduce transfusion requirements or alleviate anaemia, although it did markedly reduce mobilization of erythroid progenitors into the circulation [70]. Also, given that shocked or septic trauma patients may require exogenous noradrenaline, use of propranolol as a therapy may not be practical in such patients, since this competes with noradrenaline for the same binding site of β-adrenergic receptors.

With the hypercatecholamine state demonstrated to be an essential trigger for the post-injury changes in bone marrow dynamics, the current use of therapeutic noradrenaline for shock management would no doubt exacerbate bone marrow failure (although this has not been directly studied in humans). Use of non-catecholamine vasopressors, such as vasopressin [71], may be able to minimize the severity of progenitor loss from the bone marrow.

16.4.4 MSC Transplant

Allogeneic MSC transplantation is a potential therapy for bone marrow failure aimed at restoring the haematopoietic niche and modulating dysfunctional haemtopoietic progenitors. This is relevant to the trauma cohort, where significant stromal

cell loss has been measured in bone marrow samples [44], although the mechanism for this is not entirely clear, with post-injury mobilization from the bone marrow and recruitment to sites of injury not shown directly in humans nor in animal models. Haematopoietic bone marrow cell transplants to restore depleted HSCs have the inherent risks of graft-versus-host disease and the need for matched donors, which is not practical for the acute bone marrow failure seen in critically ill trauma patients. MSCs, however, have low immunogenicity [72] and can therefore be sourced from readily available donor tissues, such as umbilical cord blood. Animal models of trauma/haemorrhagic shock indicate that bone marrow failure is completely reversed 7 days after intravenous administration of MSCs [73]. Similarly, intravenous MSC administration in animal models of bone marrow failure (via total body irradiation) led to increases in white cell counts, haemoglobin, platelets as well as bone marrow haematopoietic progenitors [74]. Despite these promising findings from animal models, no human trials of MSC transplant in trauma patients have been undertaken. MSC transplant in critically ill cohorts, such as ARDS [75], septic shock [76] and COVID-19 [77] has been published, demonstrating safety and in some, efficacy; however, these studies are focused purely on the immunomodulatory functions of MSCs and thus no bone marrow related variables have been reported. MSC transplant has been used in non-trauma instances of bone marrow failure, including a number of pilot clinical trials/case studies in severe aplastic anaemia where partial recovery of bone marrow failure was evident (increases in HSC engraftment, circulating white blood cells, platelets and red blood cells) [74]. Similar findings have been reported at 2 year follow-up in systemic lupus erythematosus patients receiving MSCs [78]. Altogether, these findings would suggest that allogeneic MSCs are a promising therapeutic option for bone marrow failure that should be trialled in critically ill trauma patients.

16.5 Conclusion

Post-injury bone marrow failure is a complex and not yet fully understood complication in critically ill trauma patients, with our current understanding indicating that a hypercatecholamine state drives depletion of haematopoietic progenitors from the bone marrow and inhibition of erythropoiesis. This is compounded by iron restriction due to the post-injury inflammatory response. Parallel to the reduction in erythropoiesis is the increase in myelopoiesis, which becomes ineffective at infection clearance due to the rise of MDSCs. Predicting and measuring the severity of bone marrow failure is not currently standardized due to our incomplete understanding of the pathophysiology. Future trials of different targets to increase erythropoiesis show some promise for trauma patients and also provide important opportunities to further study post-injury bone marrow responses in clinical scenarios.

References

1. Nombela-Arrieta C, Pivarnik G, Winkel B, Canty KJ, Harley B, Mahoney JE, et al. Quantitative imaging of haematopoietic stem and progenitor cell localization and hypoxic status in the bone marrow microenvironment. Nat Cell Biol. 2013;15(5):533–43.
2. Morrison SJ, Scadden DT. The bone marrow niche for haematopoietic stem cells. Nature. 2014;505(7483):327–34.
3. Wang H, Leng Y, Gong Y. Bone marrow fat and hematopoiesis. Front Endocrinol. 2018;9:694.
4. Ding L, Saunders TL, Enikolopov G, Morrison SJ. Endothelial and perivascular cells maintain haematopoietic stem cells. Nature. 2012;481(7382):457–62.
5. Winkler IG, Sims NA, Pettit AR, Barbier V, Nowlan B, Helwani F, et al. Bone marrow macrophages maintain hematopoietic stem cell (HSC) niches and their depletion mobilizes HSCs. Blood. 2010;116(23):4815–28.
6. Tabarowski Z, Gibson-Berry K, Felten SY. Noradrenergic and peptidergic innervation of the mouse femur bone marrow. Acta Histochem. 1996;98(4):453–7.
7. Katayama Y, Battista M, Kao WM, Hidalgo A, Peired AJ, Thomas SA, et al. Signals from the sympathetic nervous system regulate hematopoietic stem cell egress from bone marrow. Cell. 2006;124(2):407–21.
8. Mendez-Ferrer S, Michurina TV, Ferraro F, Mazloom AR, Macarthur BD, Lira SA, et al. Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. Nature. 2010;466(7308):829–34.
9. Kunisaki Y, Bruns I, Scheiermann C, Ahmed J, Pinho S, Zhang D, et al. Arteriolar niches maintain haematopoietic stem cell quiescence. Nature. 2013;502(7473):637–43.
10. Carrelha J, Meng Y, Kettyle LM, Luis TC, Norfo R, Alcolea V, et al. Hierarchically related lineage-restricted fates of multipotent haematopoietic stem cells. Nature. 2018;554(7690):106–11.
11. Taccone A, Oddone M, Dell'Acqua AD, Occhi M, Ciccone MA. MRI "road-map" of normal age-related bone marrow. II. Thorax, pelvis and extremities. Pediatr Radiol. 1995;25(8):596–606.
12. Tavassoli M. Marrow adipose cells. Histochemical identification of labile and stable components. Arch Pathol Lab Med. 1976;100(1):16–8.
13. Takizawa H, Boettcher S, Manz MG. Demand-adapted regulation of early hematopoiesis in infection and inflammation. Blood. 2012;119(13):2991–3002.
14. Li J, Hale J, Bhagia P, Xue F, Chen L, Jaffray J, et al. Isolation and transcriptome analyses of human erythroid progenitors: BFU-E and CFU-E. Blood. 2014;124(24):3636–45.
15. Bessis M. [Erythroblastic island, functional unity of bone marrow]. Rev Hematol 1958;13(1):8–11.
16. Yokoyama T, Etoh T, Kitagawa H, Tsukahara S, Kannan Y. Migration of erythroblastic islands toward the sinusoid as erythroid maturation proceeds in rat bone marrow. J Vet Med Sci. 2003;65(4):449–52.
17. Sukhbaatar N, Weichhart T. Iron regulation: macrophages in control. Pharmaceuticals (Basel). 2018;11(4):137.
18. Bessis M, Mize C, Prenant M. Erythropoiesis: comparison of in vivo and in vitro amplification. Blood Cells. 1978;4(1–2):155–74.
19. Chasis JA, Prenant M, Leung A, Mohandas N. Membrane assembly and remodeling during reticulocyte maturation. Blood. 1989;74(3):1112–20.
20. Palis J. Primitive and definitive erythropoiesis in mammals. Front Physiol. 2014;5:3.
21. Haase VH. Regulation of erythropoiesis by hypoxia-inducible factors. Blood Rev. 2013;27(1):41–53.
22. Sanjuan-Pla A, Macaulay IC, Jensen CT, Woll PS, Luis TC, Mead A, et al. Platelet-biased stem cells reside at the apex of the haematopoietic stem-cell hierarchy. Nature. 2013;502(7470):232–6.
23. Ghosh J, Koussa RE, Mohamad SF, Liu J, Kacena MA, Srour EF. Cellular components of the hematopoietic niche and their regulation of hematopoietic stem cell function. Curr Opin Hematol. 2021;28(4):243–50.

24. Lok S, Kaushansky K, Holly RD, Kuijper JL, Lofton-Day CE, Oort PJ, et al. Cloning and expression of murine thrombopoietin cDNA and stimulation of platelet production in vivo. Nature. 1994;369(6481):565–8.
25. Behrens K, Alexander WS. Cytokine control of megakaryopoiesis. Growth Factors. 2018;36(3–4):89–103.
26. Bluteau D, Lordier L, Di Stefano A, Chang Y, Raslova H, Debili N, et al. Regulation of megakaryocyte maturation and platelet formation. J Thromb Haemost. 2009;7(Suppl 1):227–34.
27. Italiano JE Jr, Lecine P, Shivdasani RA, Hartwig JH. Blood platelets are assembled principally at the ends of proplatelet processes produced by differentiated megakaryocytes. J Cell Biol. 1999;147(6):1299–312.
28. Kaushansky K. Historical review: megakaryopoiesis and thrombopoiesis. Blood. 2008;111(3):981–6.
29. Lefrancais E, Ortiz-Munoz G, Caudrillier A, Mallavia B, Liu F, Sayah DM, et al. The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors. Nature. 2017;544(7648):105–9.
30. Metcalf D. The molecular biology and functions of the granulocyte-macrophage colony-stimulating factors. Blood. 1986;67(2):257–67.
31. Lieschke GJ, Grail D, Hodgson G, Metcalf D, Stanley E, Cheers C, et al. Mice lacking granulocyte colony-stimulating factor have chronic neutropenia, granulocyte and macrophage progenitor cell deficiency, and impaired neutrophil mobilization. Blood. 1994;84(6):1737–46.
32. Cronkite EP, Fliedner TM. Granulocytopoiesis. N Engl J Med. 1964;270:1403–8. CONCL.
33. Dancey JT, Deubelbeiss KA, Harker LA, Finch CA. Neutrophil kinetics in man. J Clin Invest. 1976;58(3):705–15.
34. Robinson WA, Mangalik A. The kinetics and regulation of granulopoiesis. Semin Hematol. 1975;12(1):7–25.
35. Groopman JE, Golde DW. The histiocytic disorders: a pathophysiologic analysis. Ann Intern Med. 1981;94(1):95–107.
36. Johnston RB Jr. Current concepts: immunology. Monocytes and macrophages. N Engl J Med. 1988;318(12):747–52.
37. Wang Y, Liu J, Burrows PD, Wang JY. B cell development and maturation. Adv Exp Med Biol. 2020;1254:1–22.
38. Zehentmeier S, Pereira JP. Cell circuits and niches controlling B cell development. Immunol Rev. 2019;289(1):142–57.
39. Osmond DG, Batten SJ. Genesis of B lymphocytes in the bone marrow: extravascular and intravascular localization of surface IgM-bearing cells in mouse bone marrow detected by electron-microscope radioautography after in vivo perfusion of 125I anti-IgM antibody. Am J Anat. 1984;170(3):349–65.
40. Slifka MK, Antia R, Whitmire JK, Ahmed R. Humoral immunity due to long-lived plasma cells. Immunity. 1998;8(3):363–72.
41. Spits H, Lanier LL, Phillips JH. Development of human T and natural killer cells. Blood. 1995;85(10):2654–70.
42. Kennedy MK, Glaccum M, Brown SN, Butz EA, Viney JL, Embers M, et al. Reversible defects in natural killer and memory CD8 T cell lineages in interleukin 15-deficient mice. J Exp Med. 2000;191(5):771–80.
43. Rosenthal MD, Moore FA. Persistent inflammation, immunosuppression, and catabolism: evolution of multiple organ dysfunction. Surg Infect. 2016;17(2):167–72.
44. Livingston DH, Anjaria D, Wu J, Hauser CJ, Chang V, Deitch EA, et al. Bone marrow failure following severe injury in humans. Ann Surg. 2003;238(5):748–53.
45. Warner MA, Hanson AC, Frank RD, Schulte PJ, Go RS, Storlie CB, et al. Prevalence of and recovery from anemia following hospitalization for critical illness among adults. JAMA Netw Open. 2020;3(9):e2017843.
46. Leliefeld PH, Wessels CM, Leenen LP, Koenderman L, Pillay J. The role of neutrophils in immune dysfunction during severe inflammation. Crit Care. 2016;20:73.

47. Kong T, Park YS, Lee HS, Kim S, Lee JW, You JS, et al. The delta neutrophil index predicts development of multiple organ dysfunction syndrome and 30-day mortality in trauma patients admitted to an intensive care unit: a retrospective analysis. Sci Rep. 2018;8(1):17515.
48. Mira JC, Brakenridge SC, Moldawer LL, Moore FA. Persistent inflammation, immunosuppression and catabolism syndrome. Crit Care Clin. 2017;33(2):245–58.
49. Manson J, Cole E, De'Ath HD, Vulliamy P, Meier U, Pennington D, et al. Early changes within the lymphocyte population are associated with the development of multiple organ dysfunction syndrome in trauma patients. Crit Care. 2016;20(1):176.
50. Salim A, Hadjizacharia P, DuBose J, Kobayashi L, Inaba K, Chan LS, et al. What is the significance of thrombocytosis in patients with trauma? J Trauma. 2009;66(5):1349–54.
51. Cook KM, Sifri ZC, Baranski GM, Mohr AM, Livingston DH. The role of plasma granulocyte colony stimulating factor and bone marrow dysfunction after severe trauma. J Am Coll Surg. 2013;216(1):57–64.
52. Hannoush EJ, Sifri ZC, Elhassan IO, Mohr AM, Alzate WD, Offin M, et al. Impact of enhanced mobilization of bone marrow derived cells to site of injury. J Trauma. 2011;71(2):283–9; discussion 9–91.
53. Loftus TJ, Mira JC, Miller ES, Kannan KB, Plazas JM, Delitto D, et al. The postinjury inflammatory state and the bone marrow response to anemia. Am J Respir Crit Care Med. 2018;198(5):629–38.
54. Xiang M, Yuan Y, Fan L, Li Y, Li A, Yin L, et al. Role of macrophages in mobilization of hematopoietic progenitor cells from bone marrow after hemorrhagic shock. Shock. 2012;37(5):518–23.
55. Beiermeister KA, Keck BM, Sifri ZC, ElHassan IO, Hannoush EJ, Alzate WD, et al. Hematopoietic progenitor cell mobilization is mediated through beta-2 and beta-3 receptors after injury. J Trauma. 2010;69(2):338–43.
56. Fonseca RB, Mohr AM, Wang L, Sifri ZC, Rameshwar P, Livingston DH. The impact of a hypercatecholamine state on erythropoiesis following severe injury and the role of IL-6. J Trauma. 2005;59(4):884–9; discussion 9–90.
57. Penn A, Mohr AM, Shah SG, Sifri ZC, Kaiser VL, Rameshwar P, et al. Dose-response relationship between norepinephrine and erythropoiesis: evidence for a critical threshold. J Surg Res. 2010;163(2):e85–90.
58. Johansson PI, Sorensen AM, Perner A, Welling KL, Wanscher M, Larsen CF, et al. Elderly trauma patients have high circulating noradrenaline levels but attenuated release of adrenaline, platelets, and leukocytes in response to increasing injury severity. Crit Care Med. 2012;40(6):1844–50.
59. Loftus TJ, Brakenridge SC, Murphy TW, Nguyen LL, Moore FA, Efron PA, et al. Anemia and blood transfusion in elderly trauma patients. J Surg Res. 2018;229:288–93.
60. Wu JC, Livingston DH, Hauser CJ, Deitch EA, Rameshwar P. Trauma inhibits erythroid burst-forming unit and granulocyte-monocyte colony-forming unit growth through the production of TGF-beta1 by bone marrow stroma. Ann Surg. 2001;234(2):224–32.
61. Sihler KC, Raghavendran K, Westerman M, Ye W, Napolitano LM. Hepcidin in trauma: linking injury, inflammation, and anemia. J Trauma. 2010;69(4):831–7.
62. Sayyadioskoie SR, Schwacha MG. Myeloid-Derived Suppressor Cells (MDSCs) and the immunoinflammatory response to injury (mini review). Shock. 2021;56:658.
63. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol. 2009;9(3):162–74.
64. Corwin HL, Gettinger A, Fabian TC, May A, Pearl RG, Heard S, et al. Efficacy and safety of epoetin alfa in critically ill patients. N Engl J Med. 2007;357(10):965–76.
65. Luchette FA, Pasquale MD, Fabian TC, Langholff WK, Wolfson M. A randomized, double-blind, placebo-controlled study to assess the effect of recombinant human erythropoietin on functional outcomes in anemic, critically ill, trauma subjects: the Long Term Trauma Outcomes Study. Am J Surg. 2012;203(4):508–16.

66. Pieracci FM, Stovall RT, Jaouen B, Rodil M, Cappa A, Burlew CC, et al. A multicenter, randomized clinical trial of IV iron supplementation for anemia of traumatic critical illness*. Crit Care Med. 2014;42(9):2048–57.
67. Katsarou A, Pantopoulos K. Hepcidin therapeutics. Pharmaceuticals (Basel). 2018;11(4):127.
68. Loftus TJ, Miller ES, Millar JK, Kannan KB, Alamo IG, Efron PA, et al. The effects of propranolol and clonidine on bone marrow expression of hematopoietic cytokines following trauma and chronic stress. Am J Surg. 2019;218(5):858–63.
69. Bible LE, Pasupuleti LV, Gore AV, Sifri ZC, Kannan KB, Mohr AM. Daily propranolol prevents prolonged mobilization of hematopoietic progenitor cells in a rat model of lung contusion, hemorrhagic shock, and chronic stress. Surgery. 2015;158(3):595–601.
70. Bible LE, Pasupuleti LV, Alzate WD, Gore AV, Song KJ, Sifri ZC, et al. Early propranolol administration to severely injured patients can improve bone marrow dysfunction. J Trauma Acute Care Surg. 2014;77(1):54–60; discussion 59–60.
71. Demiselle J, Fage N, Radermacher P, Asfar P. Vasopressin and its analogues in shock states: a review. Ann Intensive Care. 2020;10(1):9.
72. Ankrum JA, Ong JF, Karp JM. Mesenchymal stem cells: immune evasive, not immune privileged. Nat Biotechnol. 2014;32(3):252–60.
73. Gore AV, Bible LE, Livingston DH, Mohr AM, Sifri ZC. Mesenchymal stem cells reverse trauma and hemorrhagic shock-induced bone marrow dysfunction. J Surg Res. 2015;199(2):615–21.
74. Gonzaga VF, Wenceslau CV, Lisboa GS, Frare EO, Kerkis I. Mesenchymal stem cell benefits observed in bone marrow failure and acquired aplastic anemia. Stem Cells Int. 2017;2017:8076529.
75. Matthay MA, Calfee CS, Zhuo H, Thompson BT, Wilson JG, Levitt JE, et al. Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): a randomised phase 2a safety trial. Lancet Respir Med. 2019;7(2):154–62.
76. Schlosser K, Wang JP, Dos Santos C, Walley KR, Marshall J, Fergusson DA, et al. Effects of mesenchymal stem cell treatment on systemic cytokine levels in a phase 1 dose escalation safety trial of septic shock patients. Crit Care Med. 2019;47(7):918–25.
77. Xu X, Jiang W, Chen L, Xu Z, Zhang Q, Zhu M, et al. Evaluation of the safety and efficacy of using human menstrual blood-derived mesenchymal stromal cells in treating severe and critically ill COVID-19 patients: an exploratory clinical trial. Clin Transl Med. 2021;11(2):e297.
78. Wang D, Zhang H, Liang J, Wang H, Hua B, Feng X, et al. A long-term follow-up study of allogeneic mesenchymal stem/stromal cell transplantation in patients with drug-resistant systemic lupus erythematosus. Stem Cell Rep. 2018;10(3):933–41.

MOF in Pregnancy and Its Relevance to Eclampsia

17

Maria Barbagallo and Eleonora Schiappa

17.1 Introduction

The World Health Organization (WHO) defines near-miss morbidities as conditions/events that would have resulted in a maternal death during pregnancy, childbirth, or within 42 days after delivery if not for significant medical intervention [1].

The main criteria for identifying near-miss events are: multisystem failure or severe organ system dysfunction (e.g., respiratory, cardiac, renal failure), need for major intervention(s)/resuscitation (e.g., hysterectomy, intubation, intensive care unit admission, transfusion), and/or serious category of disease (e.g., severe hemorrhage, eclampsia) [2, 3].

The Centers for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynecologists (ACOG) use the term "**severe maternal morbidity (SMM)**" to describe complications occurring during pregnancy, delivery, or puerperium that may be life-threatening if not treated with adequate medical care [4], and this category includes any woman admitted to an intensive care unit (ICU) during pregnancy or puerperium who needs intensive life-saving treatment [4, 5].

17.2 Epidemiology

The Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project reported a 45% cumulative increase in SMM between 2006 and 2015 (from 101.3 to 146.6 per 10,000 delivery hospitalizations) [6]. Much of the increase was driven by an increase in blood transfusion, a marker of severe obstetric hemorrhage.

M. Barbagallo (✉) · E. Schiappa
Azienda Ospedaliero-Universitaria di Parma, Parma, Italy
e-mail: mbarbagallo@ao.pr.it

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_17

In addition, the rates of acute renal failure, shock, ventilation, and sepsis more than doubled during the time period [1].

Patient admitted to the ICU may present with numerous life-threatening complications, which may produce a sequential dysfunction of different organs and systems, leading to multiple organ failure (MOF), characterized by an unfavorable prognosis and currently considered the main cause of morbidity and mortality in the critically ill patient [7].

Although fewer than 2% of women require admission to an intensive care unit (ICU) during pregnancy or the peripartum period, both maternal and fetal mortality are high when such care is required [8]. The incidence of ICU admission for pregnant and postpartum women ranges from 0.7 to 13.5 per 1000 deliveries [9, 10].

The most common indications for ICU admission are postpartum hemorrhage and the hypertensive disorders (severe preeclampsia or eclampsia) [9]. However, all medical conditions that can complicate pregnancy may require admission to the ICU [8].

Maternal mortality, but also fetal mortality [9], is high when critical care is required, with estimates ranging from 3.4% to 14% [11].

17.3 The Concept of Multiple Organ Failure (MOF)

Emerging in 1970, the concept of MOF describes a syndrome with varying etiological factors involving simultaneous impairment of at least two organ systems [12]. Many papers were published recognizing MOF as a syndrome involving organs and systems separate from the site of the original condition, with a clinical spectrum ranging from subclinical dysfunction to irreversible failure of the organs involved [4].

Multiple Organ Dysfunction Syndrome (MODS) was defined as the "presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention." The term MOF was reserved for the most advanced stages of dysfunction. Primary MODS can occur, "as a direct result of a well-defined insult in which organ dysfunction occurs early and can be directly attributable to the insult itself," while secondary MODS develops as a consequence of the patient's response to an insult [13]. The main affected organs are lungs, liver, and kidneys, but also the central nervous system could be involved, ranging from subtle alterations in mental status to coma [7]. Derangements in gastrointestinal function, including loss of normal peristalsis and enterocytic barrier function are also common [7].

Obstetric patients are a particular unique cohort for the intensivist [2]. These patients are young and otherwise healthy; their management is challenged by concerns for altered maternal physiology diseases specific to pregnancy and fetal viability [14]. The increase in progesterone and, to a lesser extent, in estrogen (created by the placenta) is responsible for the changes in system function [15].

In literature little is published analyzing MOF in obstetric ICU patients. In a study of 74 female patients at University Medical Center in Jacksonville, Florida,

Afessa et al. found that although the mortality rate was low (2.7%), all those who died had MOF [16]. In a study of 453 obstetric intensive care admissions in Mumbai, India, Karnad et al. found 21.6% mortality for the entire series with very high mortality in patients diagnosed with MOF [17]. In a descriptive observational study Perez et al. found a 50% mortality in obstetric patients diagnosed with MOF. Early postpartum hemorrhage was the most frequent obstetric condition (32.8%), followed by preeclampsia-eclampsia (8.6%), puerperal sepsis (5.2%), and amniotic fluid embolism (3.4%). Mortality was highest, however, in patients with preeclampsia-eclampsia (60.0%), followed by amniotic fluid embolism (50%). The most frequent non-obstetric conditions were complications of sickle cell disease, which was present in 15.5% of total patients with MOF. Acute peritonitis (12.1%) and community-acquired pneumonia (8.6%) followed in order of frequency, with high mortality among those with acute peritonitis (71.4%) [4].

17.4 Score

Various systems have been developed for rating organ dysfunction. The severity of illness scoring systems are useful tools for comparing different populations, for hospital planning, and as research tools for critical illnesses. There are many tools available with a wide variety of methods of scoring. The most used include Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II, Sequential Organ Failure Assessment (SOFA), and Multiple Organ Dysfunction Score (MODS). APACHE II and SAPS II are based on routinely measured physiologic variables, whereas SOFA and MODS are organ failure-based scores [18].

The sequential Organ Failure Assessment (SOFA) Scale, in particular, rates 6 organ systems on a scale of 0–4. A score of ≥3 indicates "organ failure" and has the worst prognosis on the MODS spectrum [19]. Several studies have shown that the higher the SOFA score, the higher the mortality [4].

17.5 Management of Specific Diseases

Management of critical illness in pregnant and postwomen is best done collaboratively with subspecialties including intensivists and obstetric gynecologists [8].

17.5.1 Hemorrhage

Severe postpartum hemorrhage (PPH) is a major cause of maternal ICU admission, accounting for 11–49% of admissions and is the leading cause of maternal mortality worldwide, accounting for approximately 17% of maternal deaths [8, 20].

17.5.1.1 Definition

Primary postpartum hemorrhage is commonly defined as a blood loss over 500 mL in the first 24 h after vaginal delivery and over 1000 mL after cesarean section [21]. Secondary PPH refers to bleeding occurring between 24 h and 12 weeks after childbirth [22–24].

The traditional definition of PPH distinguishes four levels of severity of the condition: *minor PPH* when the loss is between 500 and 1000 mL; *moderate PPH*, between 1000 and 1500 mL; *severe PPH* more than 1500 mL and *massive PPH* when one or more of the following criteria are applicable: over 1500 mL of persistent blood loss and/or signs of clinical shock and/or transfusion of four or more units of concentrated red blood cells [24].

17.5.1.2 Diagnosis

Diagnosis can be difficult related to the correct quantification of blood loss [21]. In addition, the vital signs of these women, who are young, healthy, and with good cardiac reserve, may not show any change until blood loss reaches 2–3 L [21]. To maximize the accuracy of detection, it is recommended to use not only the visual estimation, but also other detection tools, including the use of transparent graduated bags for blood collection [25], the weight of blood laparotomy drapes, gauze, and patches and the systematic evaluation of the clinical signs and symptoms of maternal hypovolemia [21].

The *Shock Index* (SI) is a parameter used in clinical practice to evaluate hypovolemic shock and corresponds to the relationship between heart rate and systolic blood pressure (HR/SBP) [26]. The Obstetric Shock Index (OSI) is an indicator of hemodynamic instability useful in case of severe PPH. An OSI >1 is considered an indicator of clinical severity and a predictor of the need to transfuse the patient [27].

The adoption of the Modified Early Obstetrics Warning System (MEOWS) monitoring system for recording maternal parameters is also recommended [24].

The most common causes of postpartum hemorrhage are uterine atony due to poor myometrial contraction after delivery and abnormal placentation (e.g., placenta accreta, placental abruption, placenta previa) [21].

17.5.1.3 Management

The management of the postpartum bleeding requires a multidisciplinary approach [21]. At the beginning, resuscitation to re-establish the woman's hemodynamic conditions, monitoring of her clinical conditions, evaluation, and treatment of the causes of the bleeding must proceed simultaneously [21].

First, investigate the cause of bleeding, according to the 4 T rule (in order of frequency):

1. Tone
2. Trauma
3. Tissue
4. Thrombin

In practice, however, the checklist should follow this order:

1. Tone (90%): multistep treatment of uterine atony.
2. Trauma: identify and suture any birth canal lesions; perform an inspection/palpation of the perineum, vagina and fornix, cervix and uterus. If the patient is clinically unstable in the absence of an external bleeding, it is necessary to consider the possibility of an intrapelvic hematoma to be investigated first with ultrasound and possibly with an exploratory laparotomy.
3. Tissue: evaluate the retention of material by carrying out a careful inspection of the annexes and an ultrasound to evaluate the uterine content with any revision of the cavity, if necessary.
4. Thrombin: coagulopathy is rarely the cause of postpartum hemorrhage and is generally already known in medical history.

17.5.1.4 Management of Patients with Bleeding [21]

1. evaluate blood loss
2. evaluate the state of consciousness
3. evaluate the airways and respiratory rate and administer oxygen (10–15 L/min)
4. evaluate perfusion by monitoring blood pressure, heart rate, oxygen saturation (SpO_2)
5. place a bladder catheter to empty the bladder and monitor hourly diuresis and water balance
6. record the values of the vital parameters in the graphic cards for monitoring/alert
7. set up two large-caliber intravenous (EV) accesses (16 or 14 G): first IV line dedicated to fluids or blood components to correct hypovolemia and promote tissue perfusion and oxygen transport capacity; second EV line dedicated to treatment of uterine atony
8. carry out urgent blood sampling
9. venous and arterial blood gas analysis (EGA) for the evaluation of lactates
10. apply bimanual uterine compression, especially in case of late treatment or maternal collapse
11. consider the opportunity to transfer the woman to the operating room for anesthesia exploration
12. promptly consider the need for surgery and the administration of blood components if bleeding persists

Multidisciplinary approaches and the development and consistent application of comprehensive protocols for management of PPH have resulted in improved outcome for these life-threatening situations [28]. Besides the general principles of maintaining an adequate circulatory, a sufficient tissue oxygenation, and reversing or preventing a coagulopathy, PPH protocols include therapy options to eliminate the obstetric cause of PPH such as: uterotonic therapy, balloon tamponade [29], B-Lynch suture [30], uterine artery or internal iliac artery ligation [31], and uterine arterial embolization [32]. However, even with this large armamentarium for the

management of PPH, intractable uterine hemorrhage could be unresponsive and emergency peripartum hysterectomy (EPH) is usually the last resort [20]. EPH has been widely considered as a life-saving measure to manage intractable uterine hemorrhage, with a variable incidence, ranging from 0.2 per 1000 deliveries in developed countries to up to 4.43 per 1000 deliveries in developing countries [33].

However, even after a hysterectomy with secure surgical pedicles, a secondary coagulopathy can complicate the situation by impairing hemostasis, consequently contributing to more blood loss from pelvic floor venous plexuses and raw surfaces [34]. This type of bleeding resistant to clipping, ligating, or suturing could be successfully controlled with a pelvic packing affording correction of coagulopathy and further stabilization [34].

17.5.2 Cardiovascular Disease

Maternal cardiac disease and peripartum cardiomyopathy is a major cause of maternal morbidity and mortality that can be encountered in the intensive care unit (ICU) [8].

17.5.2.1 Peripartum Cardiomyopathy

(PPCM), also called pregnancy-associated cardiomyopathy, is a rare cause of heart failure (HF) that affects women late in pregnancy or in the early puerperium [35, 36].

Definition

PPCM is defined an idiopathic cardiomyopathy with the following characteristics [35]:

- Development of heart failure (HF) toward the end of pregnancy or within 5 months following delivery
- Absence of another identifiable cause for the HF
- Left ventricular (LV) systolic dysfunction with an LV ejection fraction (LVEF) of less than 45%. The LV may or may not be dilated.

Etiology

The real cause of PPCM remains unknown, despite many attempts to uncover a distinct etiology, but probably may be multifactorial [36].

Evidence from several studies supports the hypothesis that PPCM may develop as a result of interaction between pregnancy-related factors (e.g., late pregnancy oxidative stress) and a susceptible genetic background [36, 37].

Furthermore, during pregnancy, there is a 50% increase in blood volume and cardiac output, which results in transient LV remodeling and hypertrophy. It is possible that there is an exaggerated remodeling response with decrease in LV systolic function in women who develop PPCM. The hemodynamic stress of gestational hypertension, which is more common in women with PPCM, may contribute to the development of HF [36].

Risk Factors

The following are associated with increased risk of PPCM [36]:

- Age greater than 30 years
- African descent
- Pregnancy with multiple fetuses
- A history of preeclampsia, eclampsia, or postpartum hypertension
- Maternal cocaine abuse
- Long-term (>4 weeks) oral tocolytic therapy with beta adrenergic agonists
- Diabetes mellitus

Clinical Manifestations

PPCM is rarely seen before 36 weeks of gestation and affected patients usually present during the first month postpartum [38]. Pregnant women with other types of cardiac disease (e.g., ischemic, valvular, or myopathic) may present earlier in the antepartum period, coincident with the hemodynamic alterations during the second trimester [39].

Presentation of PPCM is variable and similar to that in other forms of systolic HF due to cardiomyopathy [35]. Patients most commonly complain of dyspnea, but also cough, orthopnea, paroxysmal nocturnal dyspnea, pedal edema, and hemoptysis [40]. Physical signs may include an elevated jugular venous pressure, a third heart sound, and a murmur of mitral regurgitation [41].

Diagnosis

An electrocardiogram (ECG) and echocardiogram should be performed in patients who are clinically suspected of having PPCM [36]. An ECG is helpful in the differential diagnosis to rule out other conditions such as myocardial infarction and pulmonary embolism [36].

The echocardiogram generally reveals a global reduction in LV systolic function with LVEF nearly always <45% [35]. The LV is frequently but not always dilated [35]. Other possible echocardiographic findings include left atrial enlargement, LV or left atrial thrombus, dilated right ventricle, right ventricular hypokinesis, mitral and tricuspid regurgitation, and rarely small pericardial effusion [42].

Other studies such as brain natriuretic peptide (BNP) levels, chest X-ray, cardiac magnetic resonance (CMR) imaging, cardiac catheterization, and endomyocardial biopsy (EMB) may be helpful in selected cases [36].

Management

Treatment of peripartum cardiomyopathy (PPCM) is largely similar to treatment for other types of heart failure (HF) [35, 43].

In women with PPCM and HF, the goals of medical therapy include [43]:

- Supplemental oxygen and assisted ventilation as needed
- Optimization of preload
- Hemodynamic support with inotropes and vasopressors if required

- Relief of symptoms
- When possible, institute chronic therapies that improve long-term outcomes

Angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, angiotensin receptor-neprilysin inhibitor, and aldosterone antagonists are to be avoided, as they are contraindicated in pregnancy [43].

17.5.3 Hypertensive Disease of Pregnancy

Hypertensive disease of pregnancy (HDP) is one of the main causes of maternal death in the world [44, 45] and is still one of the major causes of obstetric patient admissions to ICU in the world [9].

Severe morbidities associated with preeclampsia and eclampsia can lead to death, such as renal failure, stroke, heart failure, pulmonary edema, coagulopathy, and hepatic impairment [46].

The most widespread classification establishes four possible forms of hypertensive disorders during pregnancy: chronic hypertension, gestational hypertension, preeclampsia-eclampsia, and chronic hypertension with superimposed preeclampsia [47, 48]. A systematic review of data between 2002 and 2010 showed an incidence of preeclampsia ranging from 1.2% to 4.2% and of eclampsia ranging from 0.1% to 2.7%, with higher rates identified in regions of lesser socioeconomic development [49].

17.5.3.1 Preeclampsia

Preeclampsia is a multisystem progressive disorder characterized by the new onset of hypertension and proteinuria or of hypertension and significant end-organ dysfunction with or without proteinuria, in the last half of pregnancy or postpartum, in a previously normotensive patient [47, 50, 51].

Etiology

The disorder is caused by placental and maternal vascular dysfunction and always resolves after delivery [51, 52]. The most important theories about the pathophysiology of preeclampsia were integrated into two stages (preclinical and clinical) described by Redman et al. [53]. In the first stage, changes in the placental development and insufficient changes in uterine circulation are a result of hypoxia of the placental tissue, and mainly of the phenomenon of hypoxia and reoxygenation, and provide the development of oxidative stress and of excessive production of inflammatory and antiangiogenic factors [54]. In the second stage, placental dysfunction and the factors it releases damage the endothelium systemically by resulting in the appearance of hypertension and in the compromise of target organs. Glomerular changes (glomeruloendotheliosis) are the most characteristic and are responsible for the appearance of proteinuria [55, 56].

Risk Factors

A past history of preeclampsia, advanced maternal age, use of assisted reproductive technology, nulliparity, preexisting hypertension, pregestational diabetes, multifetal gestation, chronic kidney disease, prepregnancy body mass index >25, BMI >30, and some autoimmune diseases (antiphospholipid syndrome, systemic lupus erythematosus) carry the highest relative risk (RR) [57]. The association of preeclampsia with obesity may stem from the chronic state of systemic inflammation and, as the body mass index (BMI) increases, the activation of inflammatory pathways at the maternal–fetal interface is also exacerbated [58, 59].

Diagnosis

The diagnosis of preeclampsia should be made in a previously normotensive woman with the new onset of hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on at least two occasions at least 4 h apart) and proteinuria (≥300 mg/24 h or ≥1 + dipstick reading) after 20 weeks of gestation [57]. In the absence of proteinuria, the diagnosis can still be made if new-onset hypertension is accompanied by signs or symptoms of significant end-organ dysfunction [57].

A subset of women with preeclampsia are classified as manifesting the severe end of the preeclampsia spectrum (called "preeclampsia with severe features") [57]. This diagnosis is made after 20 weeks of gestation in previously normotensive women who develop [57]:

- Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg and proteinuria (with or without signs and symptoms of significant end-organ dysfunction)
- New-onset cerebral or visual disturbance, such as: photopsia (flashes of light) and/or scotomata (dark areas or gaps in the visual field); severe headache or headache that persists and progresses despite analgesic therapy; altered mental status
- Severe, persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by an alternative diagnosis or serum transaminase concentration ≥2 times upper limit of normal for a specific laboratory, or both
- <100,000 platelets/μL
- Progressive renal insufficiency (serum creatinine >1.1 mg/dL [97.3 μmol/L]; some guidelines also include doubling of serum creatinine concentration in the absence of other renal disease)
- Pulmonary edema

Management

The focus of clinical control is the prevention of maternal and perinatal morbidity and mortality through the following: guidelines on signs of disease involvement, referral and care in tertiary services with qualified neonatal care, good blood

pressure control, prevention of eclampsia or its recurrence, and early identification of laboratory abnormalities [47]. The evaluation of fetal well-being is also recommended. The combination of these actions should enable the decision of performing the delivery, the only real way to avoid the immediate progression of the disease with balance between maternal–fetal repercussions and the impact of prematurity [47, 60].

Expectant management in patients with preeclampsia is considered in the face of fetal prematurity or of the scarcity of resources for maternal and newborn support at the place of care [47].

The mathematical model called Preeclampsia Integrated and Estimated Risks (PIERS) was developed with the aim to reduce uncertainty in the decision of performing delivery [61]. It offers a predictive value to evaluate the odds of adverse outcomes within 48 h of the admission of the patient. The PIERS "risk calculator" is available online at https://pre-empt.bcchr.ca/monitoring/fullpiers and in a mobile application [61].

Fluids

The ideal fluid management approach for women with preeclampsia is unclear [62]. Fluid balance (input versus urine output plus estimated insensible losses [usually 30–50 mL/h]) should be monitored closely to avoid excessive administration, since women with preeclampsia are at risk of pulmonary edema and significant third-spacing [60]. A maintenance infusion of a balanced salt or isotonic saline solution at approximately 80 mL/h is often adequate for a patient who is nil by mouth and has no ongoing abnormal fluid losses, such as bleeding [63]. Oliguria that does not respond to a modest fluid bolus (e.g., a 300 mL fluid challenge) suggests renal insufficiency and should be tolerated to reduce the potential for iatrogenic pulmonary edema [63]. In patients with renal insufficiency, it is important to revise the maintenance infusion rate to account for the volume of fluid used to infuse intravenous medications [60].

Management of Hypertension

Severe hypertension in labor should be treated promptly with intravenous labetalol (avoid in patients with asthma) or hydralazine or oral nifedipine to prevent stroke [60]. It is important to remember that antihypertensive medications do not prevent eclampsia [60].

Seizure Prophylaxis

Although seizure is an infrequent occurrence in women without severe features of preeclampsia who do not receive seizure prophylaxis, the benefit of treatment is justifiable given the low cost and toxicity of the treatment of choice: magnesium sulfate ($MgSO_4$) and the relatively small number of patients that need to be treated to prevent one seizure [60, 64] [65]. It is important to emphasize that seizure prophylaxis does not prevent progression of disease unrelated to convulsions [60].

Since the publication of results of The Collaborative Eclampsia Trial—Magpie Trial, $MgSO_4$ is considered the drug of choice for the treatment of imminent

eclampsia and of eclampsia. Systematic reviews indicate that magnesium sulfate is safer and more effective than phenytoin, diazepam, or lithic cocktail (chlorpromazine, promethazine, and pethidine) for preventing recurrent seizures in eclampsia, in addition to being low cost, easy to administer and not causing sedation. Recently, fetal exposure to magnesium sulfate therapy has been shown to be a useful weapon in reducing cases of cerebral palsy and severe motor dysfunction in preterm infants (<32 weeks of gestation) [47].

Therefore, the use of magnesium sulfate is highly recommended for cases of imminent eclampsia, eclampsia, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, and preeclampsia with clinical and/or laboratory deterioration, including difficult-to-control hypertension [47].

Management of Thrombocytopenia

The risk of bleeding due to thrombocytopenia is generally considered to increase only when the platelet count is below 100,000/μL, and the risk increases substantially only with platelet counts below 50,000/μL. Platelet transfusion should not be used to normalize the platelet count in nonbleeding patients, as long as the platelet count is above 10,000–20,000/μL [60, 66]. However, platelets should not be withheld from a patient with potentially life-threatening bleeding or one who requires a higher platelet count to prevent bleeding in a high-risk setting, such as surgery [60, 67].

Glucocorticoid therapy does not appear to be effective in women with preeclampsia [68].

Complications of the disease are the usual indications for admitting patients with severe preeclampsia or eclampsia to the ICU. Examples include refractory hypertension, neurological dysfunction (e.g., seizures, intracranial hemorrhage, elevated intracranial pressure), renal failure, liver rupture, liver failure, pulmonary edema, the HELLP syndrome, and/or disseminated intravascular coagulation (DIC) [9].

ICU care involves managing such complications [50, 69, 70]:

- *Severe hypertension* (e.g., systolic BP ≥160 mmHg or diastolic BP ≥110 mmHg and persisting ≥15 min) is typically treated with nifedipine, labetalol, hydralazine, or nicardipine [71]. In the ICU, intravenous preparations of hydralazine and labetalol are most commonly used. Nitroprusside is contraindicated in the later stages of pregnancy due to possible fetal cyanide poisoning if used for more than 4 h.
- *Seizures* should be treated promptly with a bolus of intravenous magnesium sulfate, followed by the continuous infusion of magnesium sulfate. In addition, supportive care (e.g., recovery position, bite protection, supplemental oxygen) is indicated [8].
- *Intracerebral hemorrhage* requires immediate reversal of any coagulopathy, as well as the discontinuation of any anticoagulant or antiplatelet therapy. Antihypertensive therapy, seizure prophylaxis, and neurosurgical consultation may also be indicated [8].

- *Intracranial hypertension* can occur in any patient with severe preeclampsia or eclampsia, but patients who have had an intracerebral hemorrhage are at particularly high risk. Suspected elevated intracranial pressure should prompt elevation of the head of the bed to 30–45°, positioning of the head in a midline position to promote venous outflow through the jugular veins, avoidance of free water and dextrose-containing intravenous fluids, and neurosurgical consultation for potential intracranial pressure monitoring. Sedation and treatment of fever should be optimized. Some patients require osmotic diuresis using hypertonic saline, mannitol, and/or hyperventilation [72].
- *Pulmonary edema* may present with dyspnea or acute respiratory failure. Supportive management includes supplemental oxygen and fluid restriction. Diuresis is indicated if there is fluid overload, although this is rare because most patients are volume depleted [8].
- Management of *DIC* consists of treating the underlying cause, which is frequently placental abruption (abruptio placentae). Aggressive blood component replacement may be necessary when there is severe placental abruption [8].

17.5.3.2 Eclampsia

Eclampsia refers to the occurrence of generalized tonic-clonic seizures or coma in a pregnant woman with preeclampsia, in the absence of other neurologic conditions that could account for the seizure [51]. It is one of the most serious complications of the hypertensive disease of pregnancy [44, 47]. In a few cases, eclampsia presents as the initial condition [47].

Eclampsia occurs in 2–3% of women with preeclampsia with severe features, who are not receiving anti-seizure prophylaxis, and in up to 0.6% of women with preeclampsia without severe features [73].

In a systematic review, 59% of eclampsia occurred antepartum, 20% occurred intrapartum, and 21% occurred postpartum [74]. Approximately 90% of postpartum seizures occur within 1 week of delivery [75, 76]. Antecedent symptoms are similar to those with antepartum and intrapartum eclampsia [77] and include shortness of breath, blurry vision, nausea or vomiting, edema, neurological deficit, and epigastric pain [76, 77].

Etiology

The precise cause of eclamptic seizures is not clearly understood [77]. Two models have been proposed, based on the central role of hypertension [77]. According to the first model, hypertension causes a breakdown of the autoregulatory system of the cerebral circulation, leading to hyperperfusion, endothelial dysfunction, and vasogenic and/or cytotoxic edema. In the second model, hypertension causes activation of the autoregulatory system, leading to vasoconstriction of cerebral vessels, hypoperfusion, localized ischemia, endothelial dysfunction, and vasogenic and/or cytotoxic edema [78]. Cerebral inflammation may also play a role [79].

Risk Factors

Risk factors for eclampsia are similar to those for preeclampsia. Women at highest risk are nonwhite, nulliparous, and from lower socioeconomic backgrounds. The peak incidence is in adolescence and the early twenties, but incidence is also increased in women over age 35 [80].

Diagnosis

Eclampsia is a clinical diagnosis based on the occurrence of new-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions (e.g., epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, drug use), typically in a woman with a hypertensive disorder of pregnancy (preeclampsia, gestational hypertension, HELLP syndrome) [57].

Eclampsia is generally manifested by a generalized tonic-clonic seizure or coma. At onset, there is an abrupt loss of consciousness, often associated with a scream or shriek. The muscles of the arms, legs, chest, and back then become stiff. The woman may begin to appear cyanotic during this tonic phase. After approximately 1 min, the muscles begin to jerk and twitch for an additional 1–2 min. The tongue may be bitten; frothy, and bloody sputum may come out of the mouth [77]. The postictal phase begins once the twitching movements end. The woman is initially in a deep sleep, breathing deeply, and then gradually wakes up, often complaining of a headache.

Most patients begin to recover responsiveness within 10–20 min after the generalized convulsion. Focal neurologic deficits are generally absent [77].

Fetal bradycardia for at least 3–5 min is a common finding during and immediately after the seizure. Resolution of maternal seizure activity is associated with fetal tachycardia and loss of fetal heart rate variability, sometimes with transient decelerations [81]. The fetal heart rate pattern generally improves with maternal and fetal therapeutic interventions [77]. A nonreassuring pattern with frequent, recurrent decelerations for more than 10–15 min despite maternal and fetal resuscitative interventions suggests the possibility of an occult abruption [82].

On physical examination, neurologic findings may include memory deficits, brisk deep tendon reflexes, visual perception deficits, visual processing deficits, altered mental status, and cranial nerve deficits [77].

Differential Diagnosis of Seizures

The differential diagnosis of new-onset seizures in a pregnant woman involves determining whether the seizure was mostly incidental to the pregnant state (e.g., brain tumor, ruptured aneurysm), exacerbated by the pregnant state (e.g., thrombotic thrombocytopenic purpura [TTP], hemolytic uremic syndrome [HUS], cerebral venous thrombosis), or unique to the pregnant state (e.g., eclampsia) [77].

The following factors should be considered in differential diagnosis:

- The occurrence of preeclampsia/eclampsia before 20 weeks of gestation is rare and should raise the possibility of an underlying molar pregnancy or a cause of seizure unrelated to pregnancy. Molar pregnancy may be suspected based on the

sonographic appearance of the placenta and may occur with a coexistent normal co-twin [77].

- Persistent neurologic deficits suggest an anatomic abnormality, whether or not the woman has eclampsia. Causes of sudden development of neurologic symptoms include stroke, intracranial hemorrhage, brain mass lesion, toxic and metabolic encephalopathies, reversible cerebral vasoconstriction syndrome, thrombotic thrombocytopenic purpura (TTP), and central nervous system infection [83].
- Seizures without neurologic deficits may be triggered by metabolic abnormalities (e.g., hypocalcemia, hyponatremia, hypoglycemia), toxins (drug or alcohol withdrawal, drug intoxication), infection (meningitis, encephalitis, sepsis), or recent head trauma. History, physical examination, and laboratory studies can help distinguish these disorders from eclampsia. Laboratory tests appropriate for the evaluation of a first seizure include electrolytes, glucose, calcium, magnesium, hematology studies, renal function tests, liver function tests, and toxicology screens, although the likelihood of finding a relevant abnormality in unselected patients is low [77].
- The absence of neurologic deficits does not exclude an anatomic abnormality within the brain. Neuroimaging when the patient is clinically stable may be valuable in select cases [77].
- Pregnancy is a precipitating factor for some disorders associated with seizure activity, such as thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS). TTP and HUS may be indistinguishable from eclampsia that occurs in a woman with HELLP syndrome and approximately 10–20% of women with preeclampsia/eclampsia have laboratory findings of HELLP syndrome. Eclampsia and HELLP usually start to quickly improve after delivery, but delivery does not affect the course of TTP and HUS [77].

Management

If the seizure is witnessed, maintaining airway patency and preventing aspiration are the initial priorities. The woman should be rolled onto her left side [82].

The immediate issues include [77]:

- Prevention of maternal hypoxia and trauma
- Treatment of severe hypertension, if present
- Prevention of recurrent seizures
- Evaluation for prompt delivery

Women who do not improve promptly following control of hypertension and seizures and those who develop localizing neurologic signs should be evaluated by a neurologist [77].

Prevention of Recurrent Seizures

The anticonvulsive drug of choice is magnesium sulfate [77]. Treatment is primarily directed at prevention of recurrent seizures rather than control of the initial seizure

since the initial seizure is usually of short duration and may occur in a setting where intravenous (IV) access and drugs are not readily available [77].

Approximately 10% of women with eclampsia will have repeated seizures if managed expectantly [84]. Women with eclampsia require anticonvulsant therapy to prevent recurrent seizures and the possible complications of repeated seizure activity: neuronal death, rhabdomyolysis, metabolic acidosis, aspiration pneumonitis, neurogenic pulmonary edema, and respiratory failure. Magnesium sulfate is the drug of choice based on randomized trials demonstrating that it reduces the rate of recurrent seizures by one-half to two thirds [73].

Management of Recurrent Seizures

Recurrent seizures in patients on maintenance magnesium sulfate therapy can be treated with an additional bolus of 2–4 g magnesium sulfate administered IV over 5 min, with frequent monitoring for signs of magnesium toxicity (e.g., loss of patellar reflex, respiratory rate <12 per minute, oliguria) [77]. In cases refractory to magnesium sulfate (patient is still seizing at 20 min after the bolus or more than two recurrences), a health care provider can administer sodium amobarbital (250 mg IV over 3 min), thiopental, or phenytoin (1250 mg IV at a rate of 50 mg/min) [57]. Endotracheal intubation and assisted ventilation in the intensive care unit are appropriate in these circumstances [77].

Status epilepticus, as well as recurrent seizures while on magnesium seizure prophylaxis, should raise concerns about an intracranial lesion/stroke [77]. Although neurology consultation and head imaging are indicated in this setting, the acute management of the seizures is similar regardless of the cause of status epilepticus [77].

17.5.3.3 Hemolysis, Elevated Liver Enzymes, and Low Platelets Syndrome (HELLP Syndrome)

HELLP refer to the association of severe Hemolysis, Elevated Liver enzymes (liver impairment) and Low Platelets (platelets consumption) [44, 51].

- Hemolysis: presence of schizocytes and echinocytes in the peripheral blood and/or elevation of lactate dehydrogenase (LDH) levels >600 UI/L and/or indirect bilirubin >1.2 mg/dL and/or haptoglobin ≤0.3 g/L;
- hepatic impairment determined by elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values > twice their normal value;
- platelet count defined as <100,000/mm^3.

HELLP syndrome probably represents a subtype of preeclampsia with severe features in which hemolysis, elevated liver enzymes, and thrombocytopenia are the predominant features, rather than hypertension, central nervous system, or renal dysfunction, although the latter do occur [51].

It affects 0.5–0.9% of all pregnancies and 10–20% of parturients diagnosed with severe preeclampsia [85]. Although the diagnosis of HELLP syndrome requires evidence of hemolysis, hepatic dysfunction, and thrombocytopenia, specific diagnostic

criteria and clinical presentations vary, making the precise diagnosis challenging [85]. Furthermore, HELLP syndrome may be complicated by multiorgan dysfunction, which makes it difficult to differentiate from disseminated intravascular coagulation (DIC), pulmonary embolism (PE), amniotic fluid embolism (AFE), acute fatty liver of pregnancy (AFLP), and thrombotic thrombocytopenic purpura (TTP) [85].

17.5.3.4 Thrombotic Thrombocytopenic Purpura (TTP) and Hemolytic Uremic Syndrome (HUS)

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are systemic diseases characterized by microangiopathic hemolysis, thrombocytopenia, acute renal failure, neurological abnormalities (e.g., coma, seizures), and fever [86].

TTP is defined by a severe deficiency of ADAMTS13 (defined as activity <10%), but the initial diagnosis of TTP generally is based on clinical judgment since ADAMTS13 measures are often not available for several days [86]. Acquired, autoimmune TTP caused by antibodies to ADAMTS13 is more common than hereditary TTP due to ADAMTS13 mutation, but individuals with hereditary TTP often have the first presentation of disease during pregnancy [86].

HUS is generally characterized by acute renal failure as the dominant feature. Two major causes of HUS are Shiga-toxin producing organisms and abnormalities of complement regulation [87].

TTP and HUS are rare and potentially lethal diseases. The presentation usually occurs during the second trimester, third trimester, or early postpartum period [86]. TTP and HUS can be difficult to differentiate from preeclampsia because the clinical findings overlap and the diseases may occur simultaneously [86]. An onset of illness prior to a gestation age of 20 weeks, the presence of significant hemolysis, and/or a large elevation of lactate dehydrogenase (LDH) favors TTP or HUS. In contrast, significant hypertension, severe liver dysfunction, and/or a large elevation of aminotransferase (AST) favors preeclampsia [86]. Other diseases that should be considered whenever the diagnosis of TTP or HUS is entertained include sepsis, malignant hyperthermia, systemic lupus erythematous, and disseminated intravascular coagulation [87].

Recognition and diagnosis of TTP and HUS is important because aggressive treatment with plasma exchange improves outcome for TTP, and anti-complement therapy may rescue renal function in complement-mediated HUS [87].

17.5.4 Liver Disease

A variety of diseases may lead to liver failure during pregnancy or postpartum period [88].

The most important is the **acute fatty liver of pregnancy (AFLP)**, that is a rare pregnancy-related disease characterized by major hepatocytic fatty infiltration that usually occurs in the third trimester of pregnancy [89]. Inherited genetic mutations

in the intramitochondrial fatty acid oxidation pathway leads to microvesicular fat accumulation within hepatocytes [88].

Patients present with nausea, vomiting, right upper quadrant pain, jaundice, and increased serum aminotransferase levels (although usually not above 1000 IU/L) [88].

AFLP progression is characterized by the rapid development of acute liver failure, with hepatic coma, disseminated intravascular coagulation (DIC), and multiple organ failure [90].

The maternal mortality rate is approximately 7–18%; however, most survivors have minimal sequelae. Fetal mortality is 9–23% [88].

Treatment is delivery of the fetus, as well as supportive measures such as mechanical ventilation for coma, dialysis for renal failure, and blood products for coagulopathy [88]. In view of the underlying biochemical metabolic disorders with the accumulation of large amounts of toxic substances, some blood purification technologies have been applied to AFLP [91, 92]. Plasma exchange (PE) and plasma perfusion (PP) have been used with success in a few severe cases of AFLP [93]. Combining PE and PP may remove a large amount of toxic substances and improve clotting factors and albumin and active substance levels without the drawbacks of PE or PP alone [89].

Accumulating data indicate that timely termination of the pregnancy plus active supportive treatment can significantly reduce the maternal mortality [90, 94].

17.5.5 Acute Respiratory Failure

Acute respiratory failure requiring mechanical ventilation is a rare complication of pregnancy affecting 0.1–0.2% of pregnancies [9].

17.5.5.1 Initial Management

Initial management is the same regardless of the cause of the acute respiratory failure.

Supplemental oxygen should be administered. The preferred method of administering the oxygen depends upon the severity of the hypoxemia [95]. For patients with mild hypoxemia, administration via nasal cannula may be sufficient. More severe hypoxemia generally requires administration via a facemask, high flow nasal cannula, or a nonrebreather mask. Oxygenation should be monitored continuously by pulse oximetry. A reasonable goal for pregnant patients is to maintain the oxyhemoglobin saturation ≥95% to optimize the fetal oxygen content. Adequate fetal oxygenation requires a maternal arterial oxygen tension (PaO_2) >70 mmHg, which corresponds to an oxyhemoglobin saturation of 95% [96].

An arterial blood analysis (ABG) and chest radiograph should be obtained after initial stabilization [95].

Mechanical ventilation may be required. The decision about whether to intubate a patient should be considered in the context of pregnancy. Pregnant women have hypocapnia due to hyperventilation at baseline. Thus, the arterial carbon dioxide tension ($PaCO_2$) tends to be lower in pregnant woman than in nonpregnant

individuals with a similar degree of respiratory failure. Intubation may be difficult during pregnancy and the peripartum period due to upper airway edema and diminished airway caliber, especially late in pregnancy [95].

17.5.5.2 Differential Diagnosis

Acute respiratory failure during pregnancy or the peripartum period may be due to a conventional respiratory insult or a pregnancy-specific disorder [97–99]. The usual differential diagnosis includes the following disorders:

- Pulmonary edema
- Community-acquired pneumonia
- Aspiration
- Pulmonary embolism
- Amniotic fluid embolism
- Venous air embolism
- Acute respiratory distress syndrome (ARDS)

Pulmonary Edema

Acute pulmonary edema occurs in approximately 0.08% of pregnancies [100]. Approximately 50% of the cases of pulmonary edema were attributed to tocolytic therapy or cardiac disease. The remaining cases were ascribed to either preeclampsia or iatrogenic volume overload. Preterm labor increases the risk of pulmonary edema, likely due to the increased exposure of these patients to tocolytic therapy [95, 101].

Fluid overload is probably the major pathogenic factor in tocolytic-related pulmonary edema, although cardiac dysfunction and increased capillary permeability may also contribute [95, 102].

The clinical presentation of tocolytic-related pulmonary edema is nearly identical to that of other types of pulmonary edema: dyspnea, tachypnea, tachycardia, hypoxemia, and diffuse crackles [95]. Chest pain and a cough may also be present. The chest radiograph reveals bilateral air space disease [95].

Most patients with tocolytic-related pulmonary edema respond well to discontinuation of the tocolytic beta-2 agonist, supplemental oxygen, fluid restriction, and diuresis. Mechanical ventilation may be necessary. Most cases resolve within 12–24 h. Persistence of symptoms beyond this time period should prompt reconsideration of the diagnosis. Mortality is uncommon [95].

Pulmonary edema has also been reported to occur with the tocolytic use of the calcium channel blockers (nifedipine and nicardipine) [103, 104], and magnesium sulfate [105, 106].

Surveillance data from the United States National Hospital Discharge Survey (2004–2006) found the rate of *cardiogenic pulmonary edema* was 23 and 11 per 1000 deliveries during delivery and the postpartum period, respectively [100, 107]. Cardiogenic pulmonary edema can be a consequence of preexisting or new cardiac disease.

Pulmonary edema associated with preeclampsia and eclampsia is multifactorial [100]. Fluid overload, decreased plasma oncotic pressure, increased capillary permeability, and increased pulmonary capillary hydrostatic pressures all appear to play a role [108]. The increased hydrostatic pressure is probably due to arterial vasospasm causing elevated cardiac afterload [109, 110].

The clinical presentation of severe preeclampsia- or eclampsia-related pulmonary edema is nearly identical to that of other types of pulmonary edema [111]. These patients are hypertensive, and chest pain and/or cough may be present. The chest radiograph reveals bilateral air space disease [95].

The diagnosis is made when these findings develop in a woman who has severe preeclampsia or eclampsia in the absence of an alternative explanation for acute respiratory failure. There is no definitive diagnostic test [95].

Management of severe preeclampsia- or eclampsia-related pulmonary edema includes treatment of the severe preeclampsia or eclampsia, supplemental oxygen, and fluid restriction. Diuresis is indicated if there is fluid overload. However, clinicians must be careful to avoid compromising cardiac output and placental perfusion because many patients already have reduced cardiac preload due to intravascular depletion. Mechanical ventilation may be necessary [95].

Pneumonia

Community-acquired pneumonia is a relatively common cause of acute respiratory failure in pregnant patients. The most common pathogens are the same as those found in nonpregnant patients: Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Legionella, Chlamydia pneumoniae, and influenza A [112, 113]. However, the reduction in cell-mediated immunity that is associated with pregnancy (especially during the third trimester) also places women at increased risk for severe pneumonia and disseminated disease from atypical pathogens, such as herpesvirus, varicella, and coccidioidomycosis [114, 115]. The clinical features, diagnosis, and treatment of community-acquired pneumonia are the same for pregnant and nonpregnant patients [95].

Aspiration

Aspiration of gastric contents is most common during labor or soon after delivery. This is probably because the effects of sedation, analgesia, increased intraabdominal pressure, and recumbency are added to preexisting factors that predispose pregnant women to aspirate [95]. These factors include increased intraabdominal pressure, relaxation of the lower esophageal sphincter, and delayed gastric emptying [95]. Aspiration may also be a complication of general anesthesia and intubation during an emergent cesarean delivery [95].

Aspiration may induce chemical pneumonitis, airway obstruction, or acute bronchospasm [95].

In the case of chemical pneumonitis the treatment is supportive: supplemental oxygen, suctioning, and, if necessary, ventilatory assistance [95].

Some patients who have aspirated progress to aspiration pneumonia or acute respiratory distress syndrome (ARDS) [116].

Pulmonary Embolism

Venous thromboembolism (VTE) is the sixth leading cause of maternal death [117]. VTE can result in or complicate an ICU admission. The risk of acute pulmonary embolism (PE) is increased five to six times during pregnancy [118]. This appears to be a consequence of several factors, including changes in the clotting factors and an increased likelihood of venous stasis. Predisposing factors include obesity, an older age, a personal or family history of thromboembolic disease, inherited thrombophilia, antiphospholipid syndrome, trauma, cesarean delivery, and immobility [119].

A risk model for VTE within the first 6 weeks postpartum has been developed and externally validated, based upon two large European cohorts [120]. Among the many factors that contribute to the model, those associated with the highest risk were emergency cesarean section, stillbirth, varicose veins, preeclampsia/eclampsia, postpartum infection, and comorbidities [120].

The clinical features, diagnosis, and treatment of acute PE in women who are pregnant or peripartum are similar to those in nonpregnant individuals [8].

Clinical features include dyspnea, pleuritic chest pain, cough, leg pain and/or swelling, tachypnea, tachycardia, and hypoxemia. Circulatory collapse can occur, but it is uncommon [118].

The diagnosis of PE may be evaluated using Wells Criteria, ventilation/perfusion (*V*/*Q*) scanning, echocardiography, lung scintigraphy, Doppler venous ultrasound, and CT pulmonary angiogram (CTPA) [85].

Anticoagulation is the mainstay therapy. Once it is determined that anticoagulation is indicated, it should be initiated using subcutaneous low molecular weight heparin (LMWH), intravenous unfractionated heparin (IV UFH), or subcutaneous UFH [119]. Adjunctive therapies include supplemental oxygen and, if necessary, ventilatory assistance. Thrombolysis has been performed in the setting of circulatory collapse, but the risk of bleeding and its sequelae are high [121].

Inferior vena cava (IVC) filters have been used during pregnancy. Indications for insertion of an IVC filter are the same in pregnant and nonpregnant patients [121].

Amniotic Fluid Embolism

Amniotic fluid embolism is a rare but catastrophic illness of pregnancy and the peripartum period [85, 95]. Amniotic fluid embolism can best be described as a syndrome in a woman who is actively delivering or has recently been delivered, and it is characterized by abrupt cardiovascular collapse along with variable evidence for systemic inflammatory response syndrome and disseminated intravascular coagulation (DIC) [122].

Predisposing conditions are rapid labor, meconium-stained amniotic fluid, older maternal age, postterm pregnancy, labor induction or augmentation, eclampsia, cesarean, forceps or vacuum delivery and placental abruption or previa [123].

Symptomatic amniotic fluid embolism is relatively uncommon, perhaps 2–3 per 100,000 births [124]. Despite this, its high associated lethality makes it a preeminent problem for obstetricians [122].

The etiopathogenesis of amniotic fluid embolism is enigmatic. The prevailing theory is that tissue factor from amniotic fluid and fetal squames in meconium initiate the profound systemic inflammatory response syndrome and DIC. Whatever the cause, the immediate response is pulmonary and systemic hypertension followed quickly by hypotension, hypoxia, and coagulopathy. Cardiac arrest typically follows and is a common cause of death [122].

Survivors frequently experience adverse sequelae that include lung injury and hypoxic brain damage [122].

Management of amniotic fluid embolism includes immediate tracheal intubation with ventilatory assistance, cardiopulmonary resuscitation, and supportive measures that include improved oxygenation and circulatory support. Because of bleeding from operative sites or lacerations and uterine atony, there is usually need for rapid blood and component replacement [122].

The coagulopathy is especially problematic in women who have been or who are undergoing cesarean delivery. In undelivered women in whom cardiopulmonary resuscitation is necessary, consideration should be given for emergency cesarean delivery in an attempt to optimize these efforts. Perinatal outcomes are poor and inversely related to the maternal cardiac arrest-to-delivery interval [123].

Venous Air Embolism

Venous air embolism is an uncommon complication of pregnancy. It usually occurs during the peripartum period as a result of cesarean delivery, uterine manipulation, or central venous catheterization [125, 126].

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) may occur in pregnant women due to conditions associated with pregnancy (e.g., amniotic fluid embolism) or not associated with pregnancy (e.g., trauma). In a database analysis of pregnant women, the rate of mechanical ventilation for ARDS increased from 36.5 per 100,000 live births in 2006 to 59.6 cases per 100,000 live births in 2012 [127]. The mortality was at 9%, a rate that is lower than that reported in the general population (about 26–60%) [127].

17.5.6 Infection

Obstetrical infections may require ICU admission, particularly if they are complicated by sepsis or septic shock, which has been reported to occur in 0.002–0.04% of all deliveries [128]. Such infections are a significant cause of maternal morbidity and mortality [8]. The reported maternal mortality rate ranges from 20% to 28% in pregnant patients with septic shock and multiple organ failure [128]. Women who are black, smoke, and are older the 35 years may be more likely to be at risk of maternal sepsis [8].

The etiologies of infection during pregnancy are different in the antenatal and postnatal period:

- Antenatal infections: septic abortion, intra-amniotic infection (chorioamnionitis), complicated pyelonephritis, and pneumonias caused by Streptococcus pneumoniae and influenza [8]
- Postnatal infections: the most common is endometritis that is usually due to mixed flora (including anaerobic, gram negative, and gram positive organisms) [8]. Other postpartum infections include wound infections, necrotizing fasciitis, toxic shock syndrome, pelvic abscess, gas gangrene of the myometrium (usually due to clostridial species that colonize the gastrointestinal tract and vagina), septic pelvic thrombophlebitis, pyogenic sacroiliitis, and clostridium difficile colitis [129].

Although there are no prospective studies of early goal-directed therapy during pregnancy, the management of sepsis should be similar to that of the nonpregnant patient and use the same targets [129]. However, the SvO_2 decreases in the later stages of third trimester of pregnancy, so utilizing this target in late pregnancy may be less reliable [130]. Delivery of the fetus is determined by obstetric indications.

17.5.6.1 Toxic Shock Syndrome

Toxic shock syndrome (TSS) is an acute life-threatening disease characterized by high fever, erythematous rash with subsequent desquamation of the skin, shock, and multiple organ involvement and was first reported by Todd et al. in 1978 [131]. Although TSS has occurred predominantly in menstruating women, the proportion of cases not associated with menstruation has been increasing steadily since 1980 [132]. The removal of high-absorbency tampons from the market has decreased the incidence of menstrual TSS [132]. As a result, approximately one-half of all reported TSS cases are currently nonmenstrual [132].

Nonmenstrual TSS can occur due to the use of barrier contraceptives, vaginal and cesarean deliveries, surgical and postpartum wound infections, mastitis, septorhinoplasty (particularly when nasal packing is used), sinusitis, arthritis, burns, cutaneous and subcutaneous lesions (including abscesses, ulcers, and cellulitis), respiratory infections after influenza, and enterocolitis [132]. In most cases of TSS associated with a surgical site or wound infections, it can occur in the absence of any signs of apparent infection [132]. In most cases of TSS associated with a surgical site or wound infections, there is little or no evidence of inflammation at the site of *S. aureus* replication [132].

Current diagnostic criteria for TSS are published by the Centers for Disease Control and Prevention (CDC) [132]. There are five clinical criteria for the diagnosis of TSS: fever over 38.9 °C, rash, desquamation of the skin, hypotension, and the involvement of three or more organ systems including the gastrointestinal, muscular, mucous membranes, renal, hepatic, hematologic, and central nervous systems [132].

Early recognition of TSS is important in order to provide the appropriate therapy. This therapy should include the prompt drainage of the site to control ongoing toxin production, the use of antimicrobial therapy targeting *S. aureus* (such as clindamycin to inhibit protein synthesis and further toxin production, and vancomycin if MRSA [Methicillin resistant Staphylococcus aureus] is the causative organism), and supportive therapy including fluid resuscitation and pressor support, if required [132].

17.5.7 Disseminated Intravascular Coagulation (DIC)

Disseminated intravascular coagulation (DIC) during pregnancy is a unique entity. It is always secondary to an underlying disease or complication and subsides only when it resolves [133]. DIC represents a life-threatening condition that is the endpoint of uncontrolled systemic activation of the hemostatic system, leading to a simultaneous widespread microvascular thrombosis, that can compromise the blood supply to different organs and may lead to organ failure [134]. This process is associated with increased degradation of coagulation factors as well as anticoagulation proteins and followed by their impaired synthesis, leading to uncontrolled bleeding [134].

Acute, severe DIC is characterized by diffuse multiorgan bleeding, hemorrhagic necrosis, microthrombi in small blood vessels, and thrombi in medium and large blood vessels [134]. The final scenario is represented by the exhaustion of coagulation/anticoagulation factors and platelets, leading to profuse uncontrollable bleeding and often death [134].

During pregnancy, a substantive increase in plasma volume is concomitantly augmented by production of most procoagulants. Importantly, fibrinogen (factor I) concentration increases approximately 50% above nonpregnant values, and during late pregnancy, it ranges from approximately 375–620 mg/dL [135]. Thus, virtually all clotting factors increase [122]. At the same time, there is a reduction in levels of natural anticoagulants protein C and S and tissue factor pathway inhibitor-1 as well as an acquired resistance to protein C [136]. In addition, profibrinolysin or plasminogen levels increase but there is also increased inhibition of fibrinolysis. As a result of all of these alterations, there is a physiologic prothrombotic state during gestation [134].

The initiation of DIC begins with the release of tissue factor by any number of pathologic conditions [122]. In most cases, tissue factor is released by damaged subendothelial tissue and stimulated monocytes, which in turn provoke release of cytokines from the endothelium. In this scenario, with focal injury, there is attraction of monocytes and subendothelium with platelets that promotes localized coagulation [122]. To the contrary, with generalized endothelial activation, there is diffuse activation of coagulation [122]. Although tissue factor is found in endothelial cells, it is also in abundant supply in trophoblastic tissue and amniotic fluid [137, 138]. Thus, in obstetric syndromes, some of the most profound

coagulopathies are stimulated by release of tissue factor from these sources. This clinicopathologic phenomenon culminates in a systemic intravascular activation of coagulation that completely disrupts natural hemostasis [139]. In severe cases, this ineffective balance of natural anticoagulant mechanisms can result in widespread fibrin deposition leading to multiorgan failure [122].

The rate of DIC during pregnancy differs among cohorts and ranges from 0.03% to 0.35% [134]. The most common obstetric events that may result in DIC are placental abruption, amniotic fluid embolism, preeclampsia, eclampsia, HELLP syndrome, sepsis syndrome, AFLP, retained stillbirth, septic abortion and intrauterine infection, and massive obstetric hemorrhage [122, 134].

17.5.7.1 Diagnosis

Early and accurate recognition of DIC is the hallmark of success in the treatment of this dire complication. Unfortunately, in the majority of the cases, the diagnosis of DIC is based on the clinical assessment of the patient [134].

An important consideration in the diagnosis of coagulopathy in obstetrics is determining whether the event is related to an actual consumption of procoagulants within the intravascular tree compared with loss of procoagulants from hemorrhage or a combination of the two. A pure form of the former would be a true DIC, whereas the latter is better termed dilutional coagulopathy [122].

Over the past few decades, both national and international organizations have attempted to establish more uniform guidelines to define DIC using various scoring systems [122]. The scoring system for DIC suggested by the subcommittee of the International Society on Thrombosis and Haemostasis (ISTH DIC score) includes four widely available variables: prothrombin time, platelet count, fibrinogen level, and a fibrin-related marker (indicator for in vitro fibrin formation) [140]. A DIC Score ≥ 5 is considered to be compatible with overt DIC [140].

Because the physiological hemostatic changes occurring in pregnancy affect the application of these scores to gestation, Erez et al. have recently constructed a pregnancy modified DIC score by using only three components of the ISTH DIC score: platelet count, fibrinogen concentrations, and the PT difference [141].

Point-of-care testing using devices like thromboelastography (Haemonetics, Braintree, MA) or thromboelastometry (TEM GmBH, Munich, Germany) is useful in the obstetrical coagulopathic disorders to achieve rapid results and decide intervention. Normal ranges have been published for women at the time of delivery compared with the standard ranges [142].

One key message is that the tests should be repeated to reflect the dynamic changes on the basis of laboratory results and clinical observations [134].

17.5.7.2 Obstetric Causes of Disseminated Intravascular Coagulation

Clinical Management

In most of these pregnancy complications, DIC is associated with adverse maternal outcome including massive blood products transfusion, hysterectomy, and even

maternal death [134]. Therefore, one of the central features in the management of DIC is recognizing the concomitant, underlying disorder [122], because the correction of these is paramount to reconcile the coagulopathy [133], and also to reduce the morbidity and mortality that is associated with DIC [134].

The basic principles for treating obstetrical DIC include: management of the underlying condition that predisposes to DIC; supportive care with blood products and related measures; regular clinical and laboratory surveillance [134].

Any treatment algorithm for obstetric DIC must take into consideration simultaneous and prompt replacement of blood loss in addition to treatment of the accompanying DIC and its cause [122]. Importantly, some of the aforementioned causes of DIC have specific treatments for the underlying disorder (e.g., treatment of sepsis with drainage, débridement, and antimicrobial therapy). In other instances exclusive to obstetric conditions (preeclampsia, HELLP, placental abruption, and acute fatty liver of pregnancy) treatment includes delivery [122]. Importantly, the clinical course of many of these women with DIC is further complicated by cesarean delivery with its attendant bleeding problems. Thus, laceration repair, uterotonic agents for uterine atony, and arrest of bleeding from operative sites is an active, if not proactive, process to effect hemostasis [122].

Given the acuity and complexity often seen in these cases, these women require admission to an ICU [122].

In the majority of obstetric disorders, bleeding has a prominent role in clinical management. Globally, guidelines for management in women with coagulopathy and bleeding are based mainly on expert opinion that recommends replacement of red blood cells, procoagulant proteins, and platelets [143, 144]. A major drawback of the latter is depletion of platelets and clotting factors resulting in the dilutional coagulopathy, which may clinically indistinguishable from DIC with major bleeding. For this reason, massive transfusion protocols are typically activated when at least 4–5 units, and sometimes more, of red blood cells have been given to the patient who is still actively bleeding [145].

In addition to blood components supplied by transfusion protocols, a number of pharmacologic compounds have been used with variable success to treat DIC in nonpregnant patients (e.g., antifibrinolytic agents as tranexamic acid) [122].

17.5.8 Supportive Care

Supportive care refers to interventions that sustain life and prevent complications, but do not treat the underlying cause of the critical illness. This includes oxygenation and ventilation (e.g., supplemental oxygen or mechanical ventilation), sedation, pain control, hemodynamic support (e.g., vasopressors), monitoring, volume management (e.g., intravenous fluids or diuretics), nutritional support, stress ulcer prophylaxis, and venous thromboembolism prophylaxis [1].

17.5.8.1 Mechanical Ventilation

Most aspects of mechanical ventilation are identical for pregnant and nonpregnant women. An exception is the target arterial carbon dioxide tension ($PaCO_2$):

- Minute ventilation should be adjusted to maintain the $PaCO_2$ between 30 and 32 mmHg. This replicates normal physiology during pregnancy since pregnant women maintain a respiratory alkalosis ($PaCO_2$ is approximately 32 mmHg and arterial pH is 7.4–7.47) due to respiratory stimulation by progesterone [8].
- A $PaCO_2$ lower than 30 mmHg should be avoided because significant respiratory alkalosis may decrease uterine blood flow [146].
- Maternal hypercapnia ($PaCO_2$ >40 mmHg) causes fetal respiratory acidosis. The use of intravenous maternal bicarbonate therapy during permissive hypercapnia is controversial due to conflicting data from animal and human studies [8].
- A reasonable goal is a maternal arterial oxygen tension (PaO_2) above 65 mmHg, although the optimal oxygen tension and peripheral saturation are unknown.

17.5.8.2 Sedation

Most drugs used for analgesia, sedation, and neuromuscular blockade are capable of getting into the umbilical venous blood and fetal circulation [147]. Thus, the potential adverse effects of an agent on the fetus (including teratogenic potential) must be considered when selecting a medication. As a general rule of thumb:

- Analgesia: any opioid is acceptable. Nonsteroidal anti-inflammatory drugs should be avoided during late pregnancy because they can cause premature closure of the ductus arteriosus and oligohydramnios.
- Sedation: sedation is often required to tolerate mechanical ventilation. There are few reports comparing benzodiazepines with other anxiolytic agents during pregnancy. Midazolam is theoretically superior to lorazepam based upon the observation of teratogenic effects in animal studies of lorazepam.
- Propofol is classified as a pregnancy category B agent based upon animal data [148]. Propofol crosses the placenta and may be associated with neonatal respiratory depression. Data on the clinical use of propofol for pregnant critically ill patients is limited to case reports, so its use should be limited until more prospective data is available [148]. There are no studies evaluating the safety and effectiveness of dexmedetomidine in the critically ill obstetric patient.
- Neuromuscular blockade: use of neuromuscular blocking agents should be avoided unless the patient has refractory respiratory failure despite aggressive sedation. Minimal data are available regarding which neuromuscular blocking agent to use for pregnant patients who require it to facilitate mechanical ventilation. Cisatracurium may be preferable as a first-line agent, based upon its pregnancy risk factor rating of B and the observation that it is not affected by renal or hepatic dysfunction. In contrast, the pregnancy risk factor rating for vecuronium and pancuronium is C, and pancuronium can accumulate in the setting of hepatic dysfunction [148].

Consultation with an obstetrician and a pharmacist who specializes in the care of pregnant patients may be helpful to facilitate the use of these agents in the ICU [8]. A neonatologist should also be present at delivery because analgesics, sedatives, and neuromuscular blocking agents can cause respiratory depression in the newborn. Ventilatory support may be needed for the newborn until the effects of the drugs wear off [149].

17.5.8.3 Vasopressors

Vasopressors and inotropes can vasoconstrict uterine blood vessels, reducing fetal blood flow. Thus, other interventions should be used initially to manage hypotension, such as administration of intravenous fluids and placing the patient in the left lateral decubitus position to prevent compression of the inferior vena cava by the gravid uterus. Hypotension that persists despite these initial interventions requires vasopressor therapy, since sustained maternal hypotension decreases uterine blood flow [8]. There is a paucity of clinical studies with no consensus about which is the best vasopressor for maternal hypotension or shock due to critical illness. In addition, the 2016 sepsis treatment guidelines published by the Society of Critical Care Medicine do not specifically address the care of pregnant patients. However, following these guidelines is reasonable for the management of maternal hypotension from septic shock [150]. Thus, norepinephrine is considered the first-line vasoactive agent in pregnant patients who fail to respond to early aggressive volume resuscitation. Although norepinephrine can reduce uterine blood flow, there are no data to suggest that norepinephrine has an adverse effect on the well-being of the fetus [8, 151].

For pregnant patients with refractory shock, the best second-line agent is unknown. However, indirect evidence from randomized trials of vasopressors for hypotension caused by spinal anesthesia and the 2016 sepsis guidelines suggest that phenylephrine may a reasonable second-line agent. Animal models have shown that ephedrine, phenylephrine, norepinephrine, and epinephrine all increase maternal blood flow. In contrast, ephedrine is the only agent to increase uterine blood flow in animals; all other agents induce vasoconstriction of uterine blood vessels [152].

The benefits of *hydrocortisone* in pregnant patients with septic shock are also unstudied, although hydrocortisone is a category C agent for pregnant patients, it can be considered in patients with refractory septic shock who are poorly responsive to both aggressive fluid resuscitation and vasopressor therapy [150].

17.5.8.4 Monitoring

All women should undergo conventional ICU monitoring. This usually includes continuous assessment of the heart rate, cardiac rhythm, oxyhemoglobin saturation, and respiratory rate, as well as frequent evaluation of the blood pressure and temperature [8].

Invasive hemodynamic monitoring is occasionally helpful, especially when hypoxemic respiratory failure is accompanied by hypotension and/or renal failure. In these situations, hemodynamic measures can help determine the volume status,

which is essential for administration of the optimal balance of intravenous fluids, diuretics, and vasoactive medications [8]. Invasive hemodynamic monitoring is generally accomplished using a central venous catheter to measure the central venous pressure. Pulmonary artery catheters are rarely needed. Interpretation of hemodynamic measures must consider the expected physiologic changes of pregnancy [8]. Arterial catheterization may be helpful if the blood pressure is labile or frequent arterial blood gases are needed.

Pregnant women should have fetal heart rate and uterine monitoring, the frequency of which depends upon the gestational age of the fetus and the clinical scenario.

Bedside critical care ultrasound is emerging as a useful tool in the assessment of the hypotensive critically ill patient. Transthoracic echocardiography (TTE) may assist in the differentiation of life-threatening hypotension in the critically ill obstetric patient [153]. For example, bedside TTE allows the rapid identification of right ventricular versus left ventricular heart failure, thereby allowing the timely administration of appropriate therapy or pursuit of additional testing.

References

1. Brown HL, Small MJ. Overview of maternal mortality and morbidity. UpToDate; 2019.
2. Oliveira Neto AF, Parpinelli MA, Costa ML, Souza RT, Ribeiro do Valle C, Cecatti JG. Exploring epidemiological aspects, distribution of WHO maternal near miss criteria, and organ dysfunction defined by SOFA in cases of severe maternal outcome admitted to obstetric ICU: a cross-sectional study. Biomed Res Int. 2018;2018:5714890.
3. Adeniran AS, Bolaji BO, Fawole AA, Oyedepo OO. Predictors of maternal mortality among critically ill obstetric patients. Malawi Med J. 2015;27(1):16–9.
4. Perez A, Acevedo O, Tamayo Fdel C, Oviedo R. Characterization of obstetric patients with multiple organ failure in the intensive care unit of a Havana teaching hospital, 1998 to 2006. MEDICC Rev. 2010;12(2):27–32.
5. Kilpatrick SK, Ecker JL. Severe maternal morbidity: screening and review. Am J Obstet Gynecol. 2016;215(3):B17–22.
6. Healthcare Cost and Utilization Project. Trends and disparities in delivery hospitalizations involving severe maternal morbidity, 2006–2015. Rockville, MD: Agency for Healthcare Research and Quality; 2018. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb243-Severe-Maternal-Morbiditu-Delivery-Trends-Disparities.jsp.
7. Fink MP, Evans TW. Mechanisms of organ dysfunction in critical illness: report from a Round Table Conference held in Brussels. Intensive Care Med. 2002;28(3):369–75.
8. Clardy PF, Reardon CC. Critical illness during pregnancy and the peripartum period. UpToDate; 2019. www.uptodate.com.
9. Pollock W, Rose L, Dennis CL. Pregnant and postpartum admissions to the intensive care unit: a systematic review. Intensive Care Med. 2010;36(9):1465–74.
10. Guntupalli KK, Hall N, Karnad DR, Bandi V, Belfort M. Critical illness in pregnancy: part I: an approach to a pregnant patient in the ICU and common obstetric disorders. Chest. 2015;148(4):1093–104.
11. Vasquez DN, Das Neves AV, Vidal L, Moseinco M, Lapadula J, Zakalik G, et al. Characteristics, outcomes, and predictability of critically ill obstetric patients: a multicenter prospective cohort study. Crit Care Med. 2015;43(9):1887–97.
12. Eiseman B, Beart R, Norton L. Multiple organ failure. Surg Gynecol Obstet. 1977;144(3):323–6.

13. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003;31(4):1250–6.
14. Ashraf N, Mishra SK, Kundra P, Veena P, Soundaraghavan S, Habeebullah S. Obstetric patients requiring intensive care: a one year retrospective study in a tertiary care institute in India. Anesthesiol Res Pract. 2014;2014:789450.
15. Varon J, Acosta P. Handbook of critical and intensive care medicine. Berlin: Springer; 2010.
16. Afessa B, Green B, Delke I, Koch K. Systemic inflammatory response syndrome, organ failure, and outcome in critically ill obstetric patients treated in an ICU. Chest. 2001;120(4):1271–7.
17. Karnad DR, Lapsia V, Krishnan A, Salvi VS. Prognostic factors in obstetric patients admitted to an Indian intensive care unit. Crit Care Med. 2004;32(6):1294–9.
18. Aarvold AB, Ryan HM, Magee LA, von Dadelszen P, Fjell C, Walley KR. Multiple organ dysfunction score is superior to the obstetric-specific sepsis in obstetrics score in predicting mortality in septic obstetric patients. Crit Care Med. 2017;45(1):e49–57.
19. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707–10.
20. Touhami O, Marzouk SB, Kehila M, Bennasr L, Fezai A, Channoufi MB, et al. Efficacy and safety of pelvic packing after emergency peripartum hysterectomy (EPH) in postpartum hemorrhage (PPH) setting. Eur J Obstet Gynecol Reprod Biol. 2016;202:32–5.
21. Linee guida dell'Istituto Superiore si Sanità. Emorragia post-partum; come prevenirla, come curarla; 2016. www.snlg-iss.it.
22. Mousa HA, Blum J, Abou El Senoun G, Shakur H, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochr Database Syst Rev. 2014;(2):CD003249.
23. Diagnosis and management of postpartum hemorrhage. ACOG technical bulletin number 143 - July 1990. Int J Gynaecol Obstet. 1991;36(2):159–63.
24. American College of Obstetricians and Gynecologists. ACOG practice bulletin: clinical management guidelines for Obstetrician-Gynecologists Number 76, October 2006: postpartum hemorrhage. Obstet Gynecol. 2006;108(4):1039–47.
25. Schorn MN. Measurement of blood loss: review of the literature. J Midwif Wwomen Health. 2010;55(1):20–7.
26. Berger T, Green J, Horeczko T, Hagar Y, Garg N, Suarez A, et al. Shock index and early recognition of sepsis in the emergency department: pilot study. West J Emerg Med. 2013;14(2):168–74.
27. Le Bas A, Chandraharan E, Addei A, Arulkumaran S. Use of the "obstetric shock index" as an adjunct in identifying significant blood loss in patients with massive postpartum hemorrhage. Int J Gynaecol Obstet. 2014;124(3):253–5.
28. Shields LE, Wiesner S, Fulton J, Pelletreau B. Comprehensive maternal hemorrhage protocols reduce the use of blood products and improve patient safety. Am J Obstet Gynecol. 2015;212(3):272–80.
29. Wright CE, Chauhan SP, Abuhamad AZ. Bakri balloon in the management of postpartum hemorrhage: a review. Am J Perinatol. 2014;31(11):957–64.
30. El-Hamamy E, Wright A, B-Lynch C. The B-Lynch suture technique for postpartum haemorrhage: a decade of experience and outcome. J Obstet Gynaecol. 2009;29(4):278–83.
31. Morel O, Malartic C, Muhlstein J, Gayat E, Judlin P, Soyer P, et al. Pelvic arterial ligations for severe post-partum hemorrhage. Indications and techniques. J Visc Surg. 2011;148(2):e95–102.
32. Vegas G, Illescas T, Munoz M, Perez-Pinar A. Selective pelvic arterial embolization in the management of obstetric hemorrhage. Eur J Obstet Gynecol Reprod Biol. 2006;127(1):68–72.
33. Tapisiz OL, Altinbas SK, Yirci B, Cenksoy P, Kaya AE, Dede S, et al. Emergency peripartum hysterectomy in a tertiary hospital in Ankara, Turkey: a 5-year review. Arch Gynecol Obstet. 2012;286(5):1131–4.

34. Dildy GA, Scott JR, Saffer CS, Belfort MA. An effective pressure pack for severe pelvic hemorrhage. Obstet Gynecol. 2006;108(5):1222–6.
35. Sliwa K, Hilfiker-Kleiner D, Petrie MC, Mebazaa A, Pieske B, Buchmann E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. Eur J Heart Fail. 2010;12(8):767–78.
36. Tsang W, Lang RM. Peripartum cardiomyopathy: etiology, clinical manifestations, and diagnosis. UpToDate; 2019.
37. Nelson JL. Pregnancy, persistent microchimerism, and autoimmune disease. J Am Med Womens Assoc (1972). 1998;53(1):31–2, 47.
38. Lee W. Clinical management of gravid women with peripartum cardiomyopathy. Obstet Gynecol Clin N Am. 1991;18(2):257–71.
39. Grewal J, Siu SC, Ross HJ, Mason J, Balint OH, Sermer M, et al. Pregnancy outcomes in women with dilated cardiomyopathy. J Am Coll Cardiol. 2009;55(1):45–52.
40. Demakis JG, Rahimtoola SH, Sutton GC, Meadows WR, Szanto PB, Tobin JR, et al. Natural course of peripartum cardiomyopathy. Circulation. 1971;44(6):1053–61.
41. Desai D, Moodley J, Naidoo D. Peripartum cardiomyopathy: experiences at King Edward VIII Hospital, Durban, South Africa and a review of the literature. Trop Dr. 1995;25(3):118–23.
42. Blauwet LA, Cooper LT. Diagnosis and management of peripartum cardiomyopathy. Heart. 2011;97(23):1970–81.
43. Tsang W, Lang RM. Peripartum cardiomyopathy: treatment and prognosis. UpToDate; 2019.
44. Vasquez DN, Das Neves AV, Zakalik G, Aphalo VB, Sanchez AM, Estenssoro E, et al. Hypertensive disease of pregnancy in the ICU: a multicenter study. J Matern Fetal Neonatal Med. 2015;28(16):1989–95.
45. Organization WH. WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. Geneva: WHO; 2011.
46. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009;33(3):130–7.
47. Peracoli JC, Borges VTM, Ramos JGL, Cavalli RC, Costa S, Oliveira LG, et al. Pre-eclampsia/eclampsia. Rev Bras Ginecol Obstet. 2019;41(5):318–32.
48. ACOG. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on hypertension in pregnancy. Obstet Gynecol. 2013;122(5):1122–31.
49. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2013;170(1):1–7.
50. Usta IM, Sibai BM. Emergent management of puerperal eclampsia. Obstet Gynecol Clin N Am. 1995;22(2):315–35.
51. August P, Sibai BM. Preeclampsia: clinical features and diagnosis. UpToDate; 2019. www.uptodate.com.
52. Ngene NC, Moodley J. Role of angiogenic factors in the pathogenesis and management of pre-eclampsia. Int J Gynaecol Obstet. 2018;141(1):5–13.
53. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science. 2005;308(5728):1592–4.
54. Jauniaux E, Burton GJ. Le role du stress oxydant dans les pathologies placentaires de la grossesse [The role of oxidative stress in placental-related diseases of pregnancy]. J Gynecol Obstet Biol Reprod (Paris). 2016;45(8):775–85.
55. Meekins JW, Pijnenborg R, Hanssens M, McFadyen IR, van Asshe A. A study of placental bed spiral arteries and trophoblast invasion in normal and severe pre-eclamptic pregnancies. Br J Obstet Gynaecol. 1994;101(8):669–74.
56. Myatt L. Role of placenta in preeclampsia. Endocrine. 2002;19(1):103–11.
57. ACOG. ACOG Practice Bulletin No. 202 Summary: gestational hypertension and preeclampsia. Obstet Gynecol. 2019;133(1):211–4.

58. Walsh SW. Obesity: a risk factor for preeclampsia. Trends Endocrinol Metab. 2007;18(10):365–70.
59. Aye IL, Lager S, Ramirez VI, Gaccioli F, Dudley DJ, Jansson T, et al. Increasing maternal body mass index is associated with systemic inflammation in the mother and the activation of distinct placental inflammatory pathways. Biol Reprod. 2014;90(6):129.
60. Norwitz ER. Preeclampsia: management and prognosis. UpToDate; 2019. www.uptodate.com.
61. von Dadelszen P, Payne B, Li J, Ansermino JM, Broughton Pipkin F, Cote AM, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. Lancet. 2011;377(9761):219–27.
62. Pretorius T, van Rensburg G, Dyer RA, Biccard BM. The influence of fluid management on outcomes in preeclampsia: a systematic review and meta-analysis. Int J Obstet Anesth. 2018;34:85–95.
63. Anthony J, Schoeman LK. Fluid management in pre-eclampsia. Obstet Med. 2013;6(3):100–4.
64. Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. Lancet. 2002;359(9321):1877–90.
65. Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P. Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. Pregnancy Hypertens. 2014;4(2):105–45.
66. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 166: thrombocytopenia in pregnancy. Obstet Gynecol. 2016;128(3):e43–53.
67. Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, et al. Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2015;162(3):205–13.
68. Pourrat O, Dorey M, Ragot S, de Hauteclocque A, Deruelle P, Dreyfus M, et al. High-dose methylprednisolone to prevent platelet decline in preeclampsia: a randomized controlled trial. Obstet Gynecol. 2016;128(1):153–8.
69. Mushambi MC, Halligan AW, Williamson K. Recent developments in the pathophysiology and management of pre-eclampsia. Br J Anaesth. 1996;76(1):133–48.
70. Magann EF, Martin JN Jr. Complicated postpartum preeclampsia-eclampsia. Obstet Gynecol Clin N Am. 1995;22(2):337–56.
71. Duley L, Meher S, Jones L. Drugs for treatment of very high blood pressure during pregnancy. Cochr Database Syst Rev. 2013;(7):CD001449.
72. Frontera JA, Ahmed W. Neurocritical care complications of pregnancy and puerperum. J Crit Care. 2014;29(6):1069–81.
73. Sibai BM. Magnesium sulfate prophylaxis in preeclampsia: lessons learned from recent trials. Am J Obstet Gynecol. 2004;190(6):1520–6.
74. Berhan Y, Berhan A. Should magnesium sulfate be administered to women with mild pre-eclampsia? A systematic review of published reports on eclampsia. J Obstet Gynaecol Res. 2015;41(6):831–42.
75. Dahmus MA, Barton JR, Sibai BM. Cerebral imaging in eclampsia: magnetic resonance imaging versus computed tomography. Am J Obstet Gynecol. 1992;167(4 Pt 1):935–41.
76. Al-Safi Z, Imudia AN, Filetti LC, Hobson DT, Bahado-Singh RO, Awonuga AO. Delayed postpartum preeclampsia and eclampsia: demographics, clinical course, and complications. Obstet Gynecol. 2011;118(5):1102–7.
77. Norwitz ER. Eclampsia. UpToDate; 2019. www.uptodate.com.
78. Marra A, Vargas M, Striano P, Del Guercio L, Buonanno P, Servillo G. Posterior reversible encephalopathy syndrome: the endothelial hypotheses. Med Hypotheses. 2014;82(5):619–22.
79. Johnson AC, Tremble SM, Chan SL, Moseley J, LaMarca B, Nagle KJ, et al. Magnesium sulfate treatment reverses seizure susceptibility and decreases neuroinflammation in a rat model of severe preeclampsia. PLoS One. 2014;9(11):e113670.

80. Vousden N, Lawley E, Seed PT, Gidiri MF, Goudar S, Sandall J, et al. Incidence of eclampsia and related complications across 10 low- and middle-resource geographical regions: secondary analysis of a cluster randomised controlled trial. PLoS Med. 2019;16(3):e1002775.
81. Paul RH, Koh KS, Bernstein SG. Changes in fetal heart rate-uterine contraction patterns associated with eclampsia. Am J Obstet Gynecol. 1978;130(2):165–9.
82. Sibai BM. Diagnosis, prevention, and management of eclampsia. Obstet Gynecol. 2005;105(2):402–10.
83. Wright WL. Neurologic complications in critically ill pregnant patients. Handb Clin Neurol. 2017;141:657–74.
84. Pritchard JA, Cunningham FG, Pritchard SA. The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. Am J Obstet Gynecol. 1984;148(7):951–63.
85. Prin M, Gaffney A, Mankowitz SW. Pulmonary embolism in the setting of HELLP syndrome. Int J Obstet Anesth. 2015;24(2):184–90.
86. Fyfe-Brown A, Clarke G, Nerenberg K, Chandra S, Jain V. Management of pregnancy-associated thrombotic thrombocytopenia purpura. AJP Rep. 2013;3(1):45–50.
87. Allford SL, Hunt BJ, Rose P, Machin SJ. Guidelines on the diagnosis and management of the thrombotic microangiopathic haemolytic anaemias. Br J Haematol. 2003;120(4):556–73.
88. Tran TT, Ahn J, Reau NS. ACG clinical guideline: liver disease and pregnancy. Am J Gastroenterol. 2016;111(2):176–94; quiz 96.
89. Ding J, Han LP, Lou XP, Geng LN, Liu D, Yang Q, et al. Effectiveness of combining plasma exchange with plasma perfusion in acute fatty liver of pregnancy: a retrospective analysis. Gynecol Obstet Investig. 2015;79(2):97–100.
90. Ibdah JA. Acute fatty liver of pregnancy: an update on pathogenesis and clinical implications. World J Gastroenterol. 2006;12(46):7397–404.
91. Martin JN Jr, Briery CM, Rose CH, Owens MT, Bofill JA, Files JC. Postpartum plasma exchange as adjunctive therapy for severe acute fatty liver of pregnancy. J Clin Apher. 2008;23(4):138–43.
92. Vora KS, Shah VR, Parikh GP. Acute fatty liver of pregnancy: a case report of an uncommon disease. Ind J Crit Care Med. 2009;13(1):34–6.
93. Dovlatian AA, Bentsianov VA. Plazmaferez v lechenii oslozhnennykh form ostrogo gnoinogo pielonefrita beremennykh. [Plasmapheresis in the treatment of complicated forms of acute suppurative pyelonephritis in pregnant women]. Urol Nefrol. 1995(1):22–5.
94. Zhou G, Zhang X, Ge S. Retrospective analysis of acute fatty liver of pregnancy: twenty-eight cases and discussion of anesthesia. Gynecol Obstet Investig. 2013;76(2):83–9.
95. Clardy PF, Reardon CC. Acute respiratory failure during pregnancy and the peripartum period. UpToDate; 2019.
96. Cole DE, Taylor TL, McCullough DM, Shoff CT, Derdak S. Acute respiratory distress syndrome in pregnancy. Crit Care Med. 2005;33(10 Suppl):S269–78.
97. Mighty HE. Acute respiratory failure in pregnancy. Clin Obstet Gynecol. 2010;53(2):360–8.
98. Lapinsky SE. Acute respiratory failure in pregnancy. Obstet Med. 2015;8(3):126–32.
99. Guntupalli KK, Karnad DR, Bandi V, Hall N, Belfort M. Critical illness in pregnancy: Part II: Common medical conditions complicating pregnancy and puerperium. Chest. 2015;148(5):1333–45.
100. Sciscione AC, Ivester T, Largoza M, Manley J, Shlossman P, Colmorgen GH. Acute pulmonary edema in pregnancy. Obstet Gynecol. 2003;101(3):511–5.
101. Hatjis CG, Swain M. Systemic tocolysis for premature labor is associated with an increased incidence of pulmonary edema in the presence of maternal infection. Am J Obstet Gynecol. 1988;159(3):723–8.
102. Lamont RF. The pathophysiology of pulmonary oedema with the use of beta-agonists. BJOG. 2000;107(4):439–44.
103. Kutuk MS, Ozgun MT, Uludag S, Dolanbay M, Yildirim A. Acute pulmonary failure due to pulmonary edema during tocolytic therapy with nifedipine. Arch Gynecol Obstet. 2013;288(4):953–4.

104. Abbas OM, Nassar AH, Kanj NA, Usta IM. Acute pulmonary edema during tocolytic therapy with nifedipine. Am J Obstet Gynecol. 2006;195(4):e3–4.
105. Samol JM, Lambers DS. Magnesium sulfate tocolysis and pulmonary edema: the drug or the vehicle? Am J Obstet Gynecol. 2005;192(5):1430–2.
106. Wilson MS, Ingersoll M, Meschter E, Bodea-Braescu AV, Edwards RK. Evaluating the side effects of treatment for preterm labor in a center that uses "high-dose" magnesium sulfate. Am J Perinatol. 2014;31(8):711–6.
107. Kuklina EV, Callaghan WM. Cardiomyopathy and other myocardial disorders among hospitalizations for pregnancy in the United States: 2004-2006. Obstet Gynecol. 2010;115(1):93–100.
108. Dennis AT, Solnordal CB. Acute pulmonary oedema in pregnant women. Anaesthesia. 2012;67(6):646–59.
109. Benedetti TJ, Kates R, Williams V. Hemodynamic observations in severe preeclampsia complicated by pulmonary edema. Am J Obstet Gynecol. 1985;152(3):330–4.
110. Bauer ST, Cleary KL. Cardiopulmonary complications of pre-eclampsia. Semin Perinatol. 2009;33(3):158–65.
111. Sibai BM, Mabie BC, Harvey CJ, Gonzalez AR. Pulmonary edema in severe preeclampsia-eclampsia: analysis of thirty-seven consecutive cases. Am J Obstet Gynecol. 1987;156(5):1174–9.
112. Sheffield JS, Cunningham FG. Community-acquired pneumonia in pregnancy. Obstet Gynecol. 2009;114(4):915–22.
113. Brito V, Niederman MS. Pneumonia complicating pregnancy. Clin Chest Med. 2011;32(1):121–32.
114. Wack EE, Ampel NM, Galgiani JN, Bronnimann DA. Coccidioidomycosis during pregnancy. An analysis of ten cases among 47,120 pregnancies. Chest. 1988;94(2):376–9.
115. Harger JH, Ernest JM, Thurnau GR, Moawad A, Momirova V, Landon MB, et al. Risk factors and outcome of varicella-zoster virus pneumonia in pregnant women. J Infect Dis. 2002;185(4):422–7.
116. Duarte AG. ARDS in pregnancy. Clin Obstet Gynecol. 2014;57(4):862–70.
117. Mac KAP, Berg CJ, Liu X, Duran C, Hoyert DL. Changes in pregnancy mortality ascertainment: United States, 1999-2005. Obstet Gynecol. 2011;118(1):104–10.
118. Bennett A, Chunilal S. Diagnosis and management of deep vein thrombosis and pulmonary embolism in pregnancy. Semin Thromb Hemost. 2016;42(7):760–73.
119. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e691S–736S.
120. Sultan AA, West J, Grainge MJ, Riley RD, Tata LJ, Stephansson O, et al. Development and validation of risk prediction model for venous thromboembolism in postpartum women: multinational cohort study. BMJ. 2016;355:i6253.
121. Malhotra A, Weinberger SE. Deep vein thrombosis and pulmonary embolism in pregnancy: treatment. UpToDate; 2019.
122. Cunningham FG, Nelson DB. Disseminated intravascular coagulation syndromes in obstetrics. Obstet Gynecol. 2015;126(5):999–1011.
123. Knight M, Berg C, Brocklehurst P, Kramer M, Lewis G, Oats J, et al. Amniotic fluid embolism incidence, risk factors and outcomes: a review and recommendations. BMC Pregnan Childb. 2012;12:7.
124. Clark SL. Amniotic fluid embolism. Obstet Gynecol. 2014;123(2 Pt 1):337–48.
125. Bandi VD, Munnur U, Matthay MA. Acute lung injury and acute respiratory distress syndrome in pregnancy. Crit Care Clin. 2004;20(4):577–607.
126. Kostash MA, Mensink F. Lethal air embolism during cesarean delivery for placenta previa. Anesthesiology. 2002;96(3):753–4.
127. Rush B, Martinka P, Kilb B, McDermid RC, Boyd JH, Celi LA. Acute respiratory distress syndrome in pregnant women. Obstet Gynecol. 2017;129(3):530–5.

128. Hensley MK, Bauer ME, Admon LK, Prescott HC. Incidence of maternal sepsis and sepsis-related maternal deaths in the United States. JAMA. 2019;322(9):890–2.
129. Plante LA, Pacheco LD, Louis JM. SMFM Consult Series #47: Sepsis during pregnancy and the puerperium. Am J Obstet Gynecol. 2019;220(4):B2–B10.
130. Clark SL, Cotton DB, Lee W, Bishop C, Hill T, Southwick J, et al. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol. 1989;161(6 Pt 1):1439–42.
131. Todd J, Fishaut M, Kapral F, Welch T. Toxic-shock syndrome associated with phage-group-I Staphylococci. Lancet. 1978;2(8100):1116–8.
132. Deguchi Y, Horiuchi Y, Shojima K, Iwahashi N, Ikejima M, Ino K, et al. Postpartum methicillin-resistant staphylococcus aureus toxic shock syndrome caused by a perineal infection. Case Rep Obstet Gynecol. 2018;2018:2670179.
133. Erez O. Disseminated intravascular coagulation in pregnancy - clinical phenotypes and diagnostic scores. Thromb Res. 2017;151(Suppl 1):S56–60.
134. Erez O, Mastrolia SA, Thachil J. Disseminated intravascular coagulation in pregnancy: insights in pathophysiology, diagnosis and management. Am J Obstet Gynecol. 2015;213(4):452–63.
135. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Obstet Gynecol. 2009;114(6):1326–31.
136. Levi M, Schultz M, van der Poll T. Disseminated intravascular coagulation in infectious disease. Semin Thromb Hemost. 2010;36(4):367–77.
137. Uszynski M, Zekanowska E, Uszynski W, Kuczynski J. Tissue factor (TF) and tissue factor pathway inhibitor (TFPI) in amniotic fluid and blood plasma: implications for the mechanism of amniotic fluid embolism. Eur J Obstet Gynecol Reprod Biol. 2001;95(2):163–6.
138. Kuczynski J, Uszynski W, Zekanowska E, Soszka T, Uszynski M. Tissue factor (TF) and tissue factor pathway inhibitor (TFPI) in the placenta and myometrium. Eur J Obstet Gynecol Reprod Biol. 2002;105(1):15–9.
139. Levi M, van der Poll T. A short contemporary history of disseminated intravascular coagulation. Semin Thromb Hemost. 2014;40(8):874–80.
140. Angstwurm MW, Dempfle CE, Spannagl M. New disseminated intravascular coagulation score: a useful tool to predict mortality in comparison with Acute Physiology and Chronic Health Evaluation II and Logistic Organ Dysfunction scores. Crit Care Med. 2006;34(2):314–20; quiz 28.
141. Erez O, Novack L, Beer-Weisel R, Dukler D, Press F, Zlotnik A, et al. DIC score in pregnant women--a population based modification of the International Society on Thrombosis and Hemostasis score. PLoS One. 2014;9(4):e93240.
142. Mallaiah S, Barclay P, Harrod I, Chevannes C, Bhalla A. Introduction of an algorithm for ROTEM-guided fibrinogen concentrate administration in major obstetric haemorrhage. Anaesthesia. 2015;70(2):166–75.
143. Hunt BJ. Bleeding and coagulopathies in critical care. N Engl J Med. 2014;370(22):2153.
144. Alexander JM, Sarode R, McIntire DD, Burner JD, Leveno KJ. Whole blood in the management of hypovolemia due to obstetric hemorrhage. Obstet Gynecol. 2009;113(6):1320–6.
145. Waters JH. Role of the massive transfusion protocol in the management of haemorrhagic shock. Br J Anaesth. 2014;113(Suppl 2):ii3–8.
146. Motoyama EK, Rivard G, Acheson F, Cook CD. The effect of changes in maternal pH and P-CO2 on the P-O2 of fetal lambs. Anesthesiology. 1967;28(5):891–903.
147. Cravey RH, Reed D. Placental transfer of narcotic analgesics in man. Clin Toxicol. 1981;18(8):911–4.
148. Hilton G, Andrzejowski JC. Prolonged propofol infusions in pregnant neurosurgical patients. J Neurosurg Anesthesiol. 2007;19(1):67–8.
149. Rochow N, Kuster H, Bandt C, Hoffmann U, Fusch C. Case 1: unexpected muscular hypotonia and need for mechanical ventilation in a preterm infant. Prolonged effect of diazepam. Acta Paediatr. 2008;97(12):1602–3, 758–9.
150. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43(3):304–77.

151. Van Nimwegen D, Dyer DC. The action of vasopressors on isolated uterine arteries. Am J Obstet Gynecol. 1974;118(8):1099–103.
152. Ngan Kee WD, Khaw KS, Tan PE, Ng FF, Karmakar MK. Placental transfer and fetal metabolic effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. Anesthesiology. 2009;111(3):506–12.
153. Dennis AT. Transthoracic echocardiography in obstetric anaesthesia and obstetric critical illness. Int J Obstet Anesth. 2011;20(2):160–8.

MOF Management in Low-Resource Settings

18

Boris E. Sakakushev

18.1 Introduction

18.1.1 Learning Goals

1. To point out the basic differences of ICU of in LMICs, compared to these in high-income countries.
2. To become informed with the specific epidemiological data of MOF in LMICs.
3. Which are the most appropriate assessment tools for MOF in LMICs?
4. To define the strategies and treatment methods of MOF relevant for LMICs.
5. To outline the optimal future approaches for MOF management in LMICs.

Although technology and evidence-based medicine have improved the quality of critical care in high-income countries, these benefits have not consistently been extended to resource-limited settings. The burden of critical care is greatest in low- and middle-income countries, and the adjusted risk of in-hospital death increases in a stepwise fashion as the global national income decreases [1, 2].

The source of this disparity is multifactorial and is driven by the lack of sufficiently trained healthcare professionals, limitations in infrastructure and equipment, and severe shortages of intensive care unit (ICU) bed capacity.

Critical illness in low- and middle-income countries (LMICs) is a major component of the global burden of disease [3]. These countries have relatively younger patient populations than those of high-income countries (HICs) [4–6].

B. E. Sakakushev (✉)
RIMU/Research Institute at Medical University of Plovdiv Bulgaria, Plovdiv, Bulgaria

Department of Propedeutics of Surgical Diseases, Medical University of Plovdiv, Plovdiv, Bulgaria

University Hospital St George Plovdiv, First Clinic of General Surgery, Plovdiv, Bulgaria
e-mail: Boris.Sakakushev@mu-plovdiv.bg; http://www.unihosp.com/

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_18

Despite this, ICU patients in LMICs still have more morbidity and mortality than those in HICs largely due to limited resources and the severity of co-morbid conditions [1, 3–5].

The burden of critical illness in low-income countries is large and likely to increase with growing urbanization, emerging epidemics, and access to hospitals [7–9].

The high cost of trained healthcare workers, infrastructure, and supplies has limited the development of intensive care units (ICUs) in low-income countries. Recent epidemiological changes in global health have created a "double burden of disease" to resource-limited settings due to an increase in the prevalence of non-communicable diseases combined with lack of improvement in the long-recognized higher burden of communicable diseases, maternal and child mortality, malnutrition, and human immunodeficiency virus (HIV)-related complications [3, 10].

18.2 Definitions

MOF initially recognized by Tilney et al. in 1973, then entitled by Baue as "Multiple, Progressive, or Sequential Systems Organ Failure and defined as a syndrome by Eiseman et al. and Fry et al." as "multiple organ failure" and "multiple system organ failure," "primarily proposed as a sign of occult or uncontrolled infection," MOF currently occurs most commonly after mechanical and thermal trauma, pancreatitis, and shock.

Multiple organ dysfunction syndrome (MODS) carries a serious risk of mortality. In order to prevent it from progressing to an irreversible stage, immediate detection and treatment are crucial [11].

Multiple organ dysfunction syndrome (MODS) is defined as the progressive physiological dysfunction of two or more organ systems where homeostasis cannot be maintained without intervention [12, 13].

Low- and middle-income country: WHO Member States are grouped into income groups (low, lower-middle, upper-middle, and high) according to the World Bank analytical classification of economies calculated using the World Bank Atlas method and based on the gross national income per capita of each country [14].

For more easier understanding and less term diversion in this chapter we will use the term MOF in all textual remarks concerning MODS.

MOF is generally initiated by illness, injury, or infection, causing a state of immunodepression and hypometabolism [13]. Rather than a single event, MOF is considered a continuum where the extent of dysfunction can vary greatly from mild impairment to irreversible failure [6]. Organs most commonly affected by MOF include the heart, lungs, liver, and kidneys [15]. It is associated with significant mortality and morbidity, estimated to affect around 15% of ICU patients and contributing to about 50% of deaths in ICU [12, 13].

MOF is induced by illness, injury, or infection that triggers an unregulated systemic inflammatory response (known as systemic inflammatory response syndrome), resulting in tissue injury [16, 17].

18.3 Epidemiology of MOF in Low-Resource Setting: Morbidity Mortality, Limited Resources, Suboptimal Understandings and Politics in LMICs

MOF syndrome is a process that occurs following 7–22% of emergency operations and between 30% and 50% of operations for intraabdominal sepsis and carries a mortality that varies from 30% to 100% depending on the number of organs involved [18].

The incidence of MOF depends on the criterion used for it as there is no consensus on a single definition as the gold standard [19]. The reported incidence of MOF among critically ill trauma patients varies widely from 28% to 88% [20].

The most common trigger is sepsis, but other causes include major trauma, surgery, burns, shock, aspiration syndromes, blood transfusion complications, severe autoimmune disease, or acute heart failure or poisonings [13, 21, 22]. Sepsis is a major reason for intensive care unit (ICU) admission, also in resource-poor settings. ICUs in low- and middle-income countries (LMICs) face many challenges that could affect patient outcome [23]. Annually, there are about 20 million cases of sepsis, defined as life-threatening acute organ dysfunction caused by a dysregulated host response to infection [1] leading to more than five million deaths, with most of the burden in low- and middle-income countries (LMICs) [24, 25]. Sepsis is a preventable, life-threatening condition marked by severe organ dysfunction. In 2017, it was estimated that it had affected 49 million individuals and was related to approximately 11 million potentially avoidable deaths worldwide [14]. However the overall and region-specific estimates should be interpreted with caution, given the limited representation of data from LMICs. Sepsis mortality is often related to suboptimal quality of care, an inadequate health infrastructure, poor infection prevention measures in place, late diagnosis, and inappropriate clinical management.

While sepsis can affect any individual worldwide, significant regional disparities in incidence and mortality exist with the highest rates in lower-middle-income countries (LMICs). Approximately 20% of all-cause global deaths are due to sepsis, disproportionately affecting neonates, pregnant or recently pregnant women, and people living in low-resource settings [14]. The burden of sepsis due to high incidence and mortality is higher in LMICs, where the severe maternal outcomes represent 12-15 per 1000 live births in LMICs compared to 0.6 per 1000 live births in high-income countries.

Sepsis is a major global health threat with a high incidence and mortality, particularly in LMICs. Overall and region-specific estimates should be interpreted with caution, given the limited representation of data from LMICs. To address the lack of LMIC representation and optimize the inclusion of studies from LMICs, WHO undertook an updated and targeted systematic review and meta-analysis that confirmed the overall paucity of data in these settings (Fig. 18.1) [14].

In countries with low, low-middle, or middle sociodemographic indices (SDI) sepsis cases reach 85.0% and sepsis-related deaths worldwide account for 84.8%, particularly in sub-Saharan Africa and South-East Asia (Fig. 18.2, [14]. From [14]. Published under the CC BY 4.0 license).

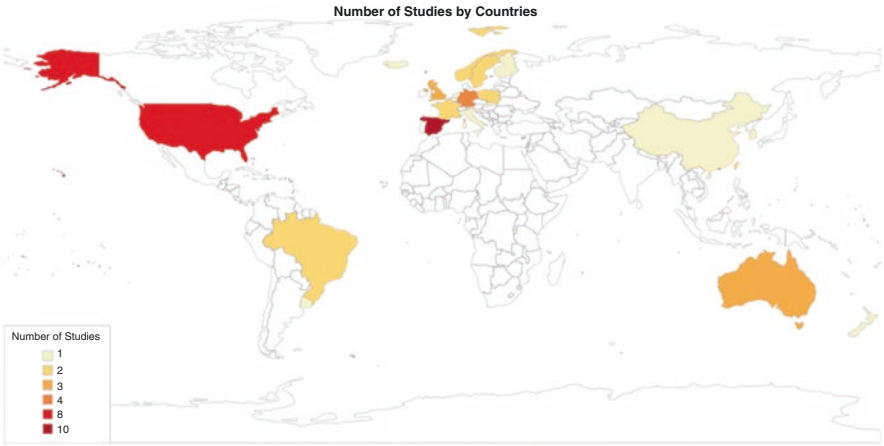


Fig. 18.1 Country-level coverage of studies on sepsis incidence

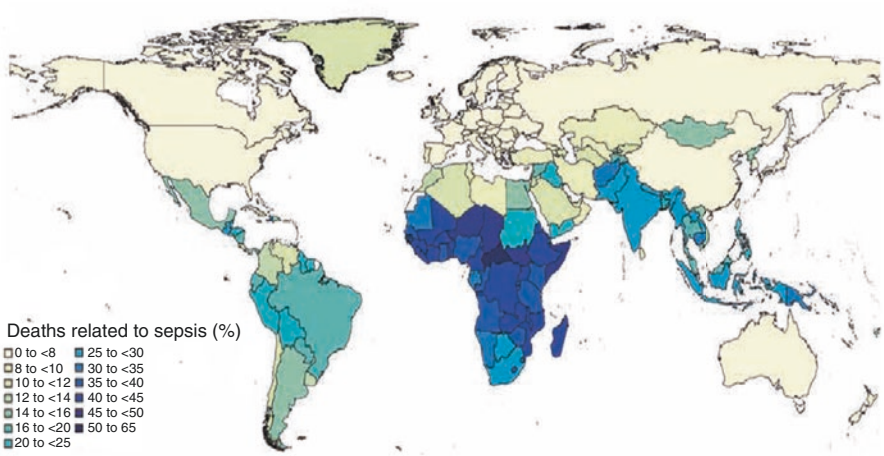


Fig. 18.2 Distribution of sepsis-related death cases worldwide in percentage. (From [14]. Published under the CC BY 4.0 license)

Trauma is a significant global health challenge, with more than five million deaths annually because of injury. Around 1.2 million deaths worldwide are due to motor vehicle collisions, and road traffic collisions are a leading cause of death and disability among the young in low- and middle-income countries (LMICs), where an estimated 90% of injury-related deaths occur [26]. Social and economic costs are the highest for these developing societies like Latin America, Central Africa, and South Asia having remarkably high death and disability rates due to social violence

and road traffic incidents and the actual social and economic cost of trauma is often difficult to quantify due to the lack of robust epidemiological data in many world regions [27, 28].

MOF remains a leading cause of morbidity and mortality in ICU settings with an enormous burden on healthcare resources. Age, presence of peritonitis, diabetes mellitus, elevated serum lactate; central venous pressure, unplanned surgery, tachycardia, and initial blood pH are the major predictors of MOF-related mortality in high-risk noncardiac surgery patients. Therefore, the identification of potential preventable predisposing factors of MOF could assist in better prognosis [29]. Globally, crude ICU mortality rates range from 9.3% in North America and 15.5% in Western Europe to 32.9% in Nigeria and 50.4% in Ethiopia [30, 31]. Reported mortality rates in critical care units are high (40–80%) in LMICs, especially among ventilated patients [32, 33]. MOF is considered as the frequent cause of mortality in patients admitted to the surgical ICU and the rate of mortality and length of hospital stay correlated with the number of organs involved and the severity of MOF [7]. An earlier study reported 15% mortality among high-risk surgical patients admitted to the ICU, of which more than half the patients died primarily due to MOF [34]. Epidemiologic studies show higher in-hospital mortality rates for critically ill patients in LMICs as compared with patients in high-income countries (HICs). Recent findings suggest that critical care interventions that are effective in HICs may not be effective and may even be harmful in LMICs. Little data on long-term and morbidity outcomes exist. Better outcomes measurement is beginning to emerge in LMICs through decision support tools that report process outcome measures, studies employing mobile health technologies with community health workers, and the development of context-specific severity of illness scores [35].

ICU beds in low-income and middle-income countries (LMICs) are limited and also have limited human and structural resources, where the working force has been described to be the costliest factor [36]. Costs for intensive care in LMICs are one-third from the cost reported from high-income countries. Alternative options for intensive care delivered outside are Rapid-Response Systems and Medical Emergency Teams.

In their systematic review of 43 studies from 15 low-income countries describing 36 individual ICUs in 31 cities, of which 16 had population greater than 500,000, and 14 were capital cities Murthy et al. found out that low-income countries lack ICU beds, and more than 50% of these countries lack any published data on ICU capacity (Fig. 18.3, [37]). Most ICUs in low-income countries are located in large referral hospitals in cities. A central database of ICU resources is required to evaluate health system performance, both within and between countries, and may help to develop related health policy.

Substantial gaps remain regarding data availability from low- and middle-income countries, the lack of community-based studies and inherent limitations of epidemiological research based on administrative data, limiting our understanding of temporal trends and geographical disparities [38].

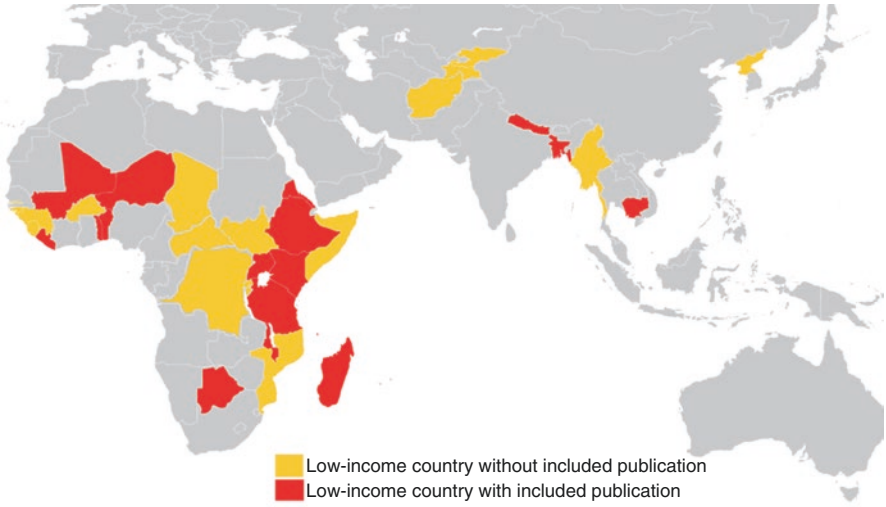


Fig. 18.3 Thirty-six low-income countries included in the search strategy with (n = 15, red) and without (n = 21, yellow) published data on ICU resource availability. (From [37]. Distributed under the terms of the Creative Commons Attribution License)

18.4 Assessment Tools of MOF in Low-Resource Settings: Scales and Grades

The Assessment of Multiple Organ Dysfunction Syndrome requires systems head-to-toe clinical examination, documentation, and analysis usually by SOFA score, where mild or severe dysfunction of at least two organs in addition to systemic inflammatory response syndrome is evaluated. The organ dysfunction may present as: acute kidney injury or uremic acidosis, acute respiratory distress syndrome, cardiomyopathy, encephalopathy, acute neurological, gastrointestinal, hepatic dysfunction, or coagulopathy [13]. The patient display relevant symptoms, depending on the affected organs [2] and the systemic inflammatory response syndrome present [11, 39, 40].

Critical care is expanding in low- and middle-income countries (LMICs) where the majority of ICUs are concentrated in large referral hospitals in urban areas [37, 41, 42]. Due to factors such as missing data and different disease patterns, predictive scores often fail to adequately predict the high rates of mortality observed [43].

Multiple mortality prediction models have been developed or validated in low- and middle-income countries (LMICs) over the last 5 years [44, 45]. The proposed uses of these models include identifying patients at acute risk for deterioration in order to trigger increased levels of care, more informed allocation of scarce resources, benchmarking for quality assessment and quality improvement and controlling for severity of illness (SOI) in future trials [46–51].

The modified early warning score (MEWS) first reported in the UK in 2001 was created by assigning weighted scores to each vital sign based on severity of the vital sign abnormality, and it has since been tested in multiple LMIC sites. MEWS includes five variables, with scores between 0 and 3 assigned for each variable [52].

The quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) score was developed as part of an international re-defining of sepsis, using high-income country (HIC) hospital administrative data 19 and retrospectively tested in nine sites in LMICs [24]. qSOFA was also prospectively tested in a study from an upper middle-income country with multiple sites [53]. qSOFA includes three variables, with 1 point given to each abnormal value, a maximum score of 3 and ≥2 considered high risk.

The Universal Vital Assessment (UVA) score was recently developed using linear regression in 15 in-hospital cohorts from six African countries and showed good predictive capability across the entire derivation population, with no reporting on its performance in the individual cohorts [47]. UVA includes seven variables, with variable points given for each abnormality. It yields a maximum score of 13, with >4 considered high risk based on its derivation study.

All three scores use accessible bedside clinical measures and are, therefore, appealing for LMIC settings where laboratory values and detailed comorbidity histories are often not available. All three scores have also been developed for hospital ward patients, which is relevant to LMICs, where critically ill patients often remain in general wards due to the scarcity of intensive care unit (ICU) beds.

In their prospective observational trial in 2017, Klinger et al. found modest predictive power of adjusted MEWS, qSOFA, and UVA scores in 647 patients with suspected infection at a Rwandan tertiary hospital, where the overall, increasing scores for adapted MEWS, qSOFA, and UVA corresponded with increasing mortality [54].

A prospective cohort study on the prognostic accuracy of the qSOFA-lactate for prediction of in-hospital mortality criteria conducted in 2017 on 1213 adult patients with suspected bacterial infection visiting the emergency department of the Indonesian National Referral Hospital has demonstrated that it is as good as the SOFA score in the emergency department of a hospital with limited resources [55].

The Sepsis-3 definition provides a change of two or more scores from zero or a known baseline of the Sequential Organ Failure Assessment (SOFA) as criteria of sepsis. A 10 year retrospective cohort study on 2350 sepsis patients in a teaching hospital in Thailand was conducted to compare the SOFA score and the quick SOFA (qSOFA) to Systemic Inflammatory Response Syndrome (SIRS) criteria in predictive ability of mortality and organ failure. The all-cause hospital mortality rate was 44.5%. The SOFA score presented the best discrimination with an area under the receiver operating characteristic curve (AUC) of 0.839. The AUC of SOFA score for hospital mortality was significantly higher than qSOFA (AUC 0.814, $p = 0.003$) and SIRS (AUC 0.587, $p < 0.0001$). The SOFA score had superior performance than other scores for predicting intensive care unit (ICU) mortality and organ failure and is a better prognostic tool for predicting mortality and organ failure than qSOFA and SIRS criteria among sepsis patients admitted to the ICU [45].

In their large prospective multicenter study in a middle-income country, among ED in 54 hospitals on 4711 ward patients with sepsis, qSOFA showed low sensitivity for the detection of patients who would die as screening tool with high percentage of missed cases of high mortality rates. Alternative approaches to prompt sepsis alerts, such as modifying qSOFA, adding lactate to a qSOFA score greater than or equal to 1, or using a single organ dysfunction, may minimize this issue [53].

A scarce number of studies available in resource-limited regions illustrate potential for the use of qSOFA, but also high variation in performance, especially regarding sensitivity. Moreover, several studies in high-income settings observed limited sensitivity of qSOFA, so its added value compared with commonly used scores for diagnosis and risk stratification of sepsis, such as the systemic inflammatory response syndrome (SIRS) criteria [12] and Modified Early Warning Score (MEWS), 13 has been questioned [56–59].

In 339 patients admitted to the ED with septic shock, Baig et al. found out that the AUROC for predicting mortality was greater for qSOFA score (AUROC cutoff = 0.89 with 95% CI; 0.85–0.92, sensitivity = 92% and specificity = 85%) when compared to SOFA score (AUROC cutoff = 0.63 with 95% CI; 0.55–0.70, sensitivity = 70%, specificity = 59%). They concluded that qSOFA score appears to be an effective tool at predicting in-hospital mortality in comparison to SOFA score when applied to severe sepsis and septic shock patients in the setting of a tertiary care hospital ED of a low-middle income country [60]. However, it is still necessary to rigorously evaluate its applicability in settings outside the ICU environment before concluding its utility beyond what it was designed for.

Recently, a new risk stratification score, the Universal Vital Assessment (UVA) score, based on data from hospital-based cohort studies in sub-Saharan Africa, and thus potentially more suited to the African setting, was developed. An amalgamated qSOFA score applying the UVA thresholds for blood pressure and respiratory rate improved predictive ability in Gabon having the best predictive ability [52].

In the analysis of 6569 adults with suspected infection admitted to 17 hospitals in ten countries in sub-Saharan Africa, Asia, and America, Rudd et al. studied the association between the quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) score and excess hospital mortality, as a marker of sepsis or analogous severe infectious course. They found out that qSOFA score greater than or equal to 2 was significantly associated with increased likelihood of excess hospital death compared with a lower score (odds ratio, 3.6), concluding that the qSOFA score may help identify patients at higher risk for excess hospital mortality among adults with suspected infection in LMICs [49].

In their prospective, observational cohort study of 118 patients Sendagire et al. studied the modified SOFA (mSOFA) score for assessing organ dysfunction and predicting mortality in a tertiary hospital ICU of a low income country. Their results confirm that calculation of the mSOFA score, ranging from 0 (normal organ function) to 24 (worst organ dysfunction), calculated on admission (T0) and at 48 h (T48) is feasible for an ICU population in a low-income country [61].

The analysis of mortality prediction models on approximately 1000 patients for 2.5 years period 2015–2017 concluded by Lukoko et al. showed that 48-h SOFA

performed significantly better in predicting outcomes among critically ill patients admitted to the ICU than admission SOFA, MPM-III, and delta-SOFA [62]. They suggested that achieving good outcomes in intensive care depends on more than the provision of world-class resources. Policies for fair allocation of beds, protocol-driven admission criteria, and appropriate patient selection could contribute to lowering the risk of mortality among the critically ill to a level on par with well-resourced ICUs in HICs.

Investigating the Modified Early Warning Score (MEWS) on 452 patients in Uganda as a triage tool to identify patients at greatest risk of death. Kruisselbrink et al. demonstrated the need for resource-suitable, setting-specific management plans, as the proportion of ward patients with MEWS of 5 or greater will exceed the physical critical care capacity at ICU and other low-resource hospital settings [63]. Possible strategies include cohorting of less stable patients to enable closer monitoring and earlier intervention. MEWS provides a systematic triage tool that enables identification of patients in need of such interventions, potentially preventing the need for ICU admission, and decreasing mortality.

In their first performance-test of an ICU risk prediction and new context-specific model in a low-income setting on Rivielo et al. developed a new Rwanda Mortality Probability Model (R-MPM) for use in low-income countries studying Rwanda's two public ICUs between August 19, 2013 and October 6, 2014 with 427 critically ill patients with mortality rate of 48.7% [51]. It demonstrated better fit to their population and had a lower data collection burden than models developed in high-income countries. After validation the R-MPM could be an alternative risk prediction model with fewer variables, better predictive power, and potential to improve the reliability of comparisons used for critical care research and quality improvement initiatives in low-income countries.

Although predictive models are recommended to undergo regional customizations, the models often do not apply to resource-constrained settings [64].

Models that have been developed for LMICs have rarely been assessed or validated in other similar settings. As predictive models are developed, these should also be examined and validated in resource-constrained settings [65].

In the prospective cohort study on 300 mechanically ventilated patients conducted in 2016–2017, with overall mortality rate of 60.7% Parker et al. assessed discrimination and calibration of multiple previously described models: Acute Physiology and Chronic Health Evaluation (APACHE) II, Sequential Organ Failure Assessment (SOFA) and quick Sequential Organ Failure Assessment (qSOFA), Simplified Acute Physiology Score (SAPS) II, Rwanda Mortality Predictive Model (R-MPM) (developed and validated in Rwanda), Vitals score (validated in Tanzania), Vitals Score For Sepsis (validated in Uganda), Tropical Intensive Care Score (TropICS), and Modified Early Warning Score (MEWS) [43]. These models were selected due to their frequency in critical care literature (APACHE II, SOFA and qSOFA, SAPS II, MEWS) or the comparability with our resource-constrained setting (R-MPM, TropICS). The authors found out that scores adapted for similar settings had similar or better predictive value than those developed in high-resource settings, but with better calibration. Further delineation of patient disease could

improve predictive scores, however, this must be balanced with ease of use and applicability of the score to the setting, requiring intensivists to use common language and scores.

Mortality prediction models could be useful in resource-limited settings to assess the impact of interventions, to assist in determining cost-effectiveness of capacity-building efforts, and to support institutional development of triage protocols [66].

18.5 Current Management of MOF in Low-Resource Settings: Algorithms, Consensus Statements, Guidelines, Recommendations

MOF can rapidly increase in severity and in the later stages the affected organs may completely lose function, reaching a mortality risk of 80–96% possibly being not reversible. Therefore preventing MOF from progressing into organ failure is crucial [21].

Back in 1998 Mervyn Singer pointed out the emphasis on prevention of organ dysfunction, including maintenance of tissue oxygenation, nutrition, and infection control stating that no definitive treatment exists despite considerable efforts to find a "magic bullet" and management of MOF still revolve around support of organ function and prevention of iatrogenic complications until recovery occurs [67].

Management of MOF aims at identifying and treating the underlying causes, comorbidities, or complications. They include fluid resuscitation to increase perfusion; multi-organ support care and monitoring: mechanical or non-invasive ventilation; maintaining fluid homeostasis; renal replacement therapy [13, 68, 69]. Maintaining an accurate fluid balance chart is important for continuous patient monitoring and recognizing possible issues [6].

To describe differences between resource-poor and resource-rich settings regarding the epidemiology, pathophysiology, economics, and research aspects of sepsis, Schultz et al. studied it in ICU setting even knowing that many sepsis patients in LMICs are treated outside an ICU. They defined two major differences: First, the resistance patterns to antimicrobial drugs can be very different, although many bacterial pathogens causing sepsis in LMICs are similar to those in high-income countries and causes of sepsis in LMICs often include tropical diseases in which direct damaging effects of pathogens and their products can sometimes be more important than the response of the host. Second, ICU capacities around the world have substantial and persisting differences, with heterogeneity within individual LMICs, where lowest capacities are to be found [23]. Although many aspects of sepsis management developed in rich countries are applicable in LMICs, implementation requires strong consideration of cost implications and the important differences in resources. Positive patient outcomes rely on immediate recognition, ICU admission, and invasive organ support [70].

Opportunities for research in epidemiology, diagnosis, therapeutics, and implementation of critical care resources in resource-limited settings can focus on burden of the disease like the The Global Burden of Disease project, which has the goal of

identifying risk factors and estimating the health impact of different diseases [71]. Another research target is the early recognition and treatment of critical illnesses in resource-limited settings focusing on, by developing tools and interventions for early detection and treatment of mainly ARDS syndrome and septic shock that could prevent multi-organ failure and death and ease burden on limited ICU resources. Conducting local QI projects in resource-limited settings, using small samples to test changes in outcomes and measuring impact on processes of care, is essential.

Until sufficient research from resource-limited settings drives locally generated clinical guidelines, adaptation of existing guidelines is essential to bring safe, feasible, and effective practices to the bedside. The Global Intensive Care Working Group of the European Society of Critical Care Medicine including experts from both resource-rich and resource-limited settings has developed recommendations for infrastructure and ICU organization in resource-limited settings and adapted recommendations for the management of sepsis in resource-limited settings. Topics covered include ventilatory support, sepsis recognition, and sepsis management in adults and children [72–75].

In their systematic review to evaluate and compare the accuracy of pre-hospital triage tools for major trauma Gianola et al. found out that the adoption of an accurate pre-hospital triage tool like Northern French Alps Trauma System (TRENAU) and New Trauma Score (NTS), best for adults, may help to allocate trauma patients according to hospital resources [76]. It is of paramount importance to match the right patient with the right hospital to maximize the healthcare and to minimize costs.

The WSES proposed the Timing of Acute Care Surgery (TACS) classification to prioritize patients admitted in the ED with a potentially surgical condition, based on simple hemodynamic and clinical data, assists in evaluating patients when multiple patients require emergency surgery or limited resources are available (Fig. 18.4, [77]). In this COVID-19 pandemic, these criteria could guide the acute surgical teams to properly tag each patient to the timing of surgery.

Critical care prognostic models are widely used in HICs for benchmarking, stratification of patients for research, and to assess quality improvement initiatives. Their applicability in LMICs is limited by the inclusion of relatively expensive laboratory parameters, diversity of case-mix, diversity of pathogenesis, the requirement for rigorous coding for diagnostic categorization, and the difficulties in systematic data gathering in the absence of electronic records.

Current critical care prognostic models are predominantly developed in high-income countries (HICs) and may not be feasible in intensive care units (ICUs) in lower- and middle-income countries (LMICs). Existing prognostic models cannot be applied without validation in LMICs as the different disease profiles, resource availability, and heterogeneity of the population may limit the transferability of such scores. A major shortcoming in using such models in LMICs is the unavailability of required measurements. This study proposes a simplified critical care prognostic model for use at the time of ICU admission [50]. In their prospective study of 3855 patients admitted to 21 ICUs from Bangladesh, India, Nepal, and Sri Lanka testing a simplified, general critical care prognostic model developed for

Timing-iTTS from diagnosis	Possible Clinical Scenarios (TACS)	Color code	Note
Immediate surgery	Bleeding emergencies		Immediate life saving surgical intervention, resuscitative laparotomy
Within an hour	Incarcerated hernia, perforated viscus, diffuse peritonitis, soft tissue infection accompanited with sepsis		Surgical Intervention as soon as possible but only after resuciation (within 1 to 2 hours). administration of antibiotics upon diagnosis- no delay
Within 6 hours	Soft tissue infection (abscess) not accompanied with sepsis		Administration of antibiotics upon diagnosis- no delay
Within 12 hours	Appendicitis (local peritonitis), cholecystitis (optinal)		Administration of antibiotics upon diagnosis- no delay
Within 24 or 48 hours	Second-look laparotomy		Schedule in advance. Intervention should occur during day time

Fig. 18.4 Timing of Acute Care Surgery (TACS) classification. (From [77]. Published under the CC BY 4.0 license)

South Asia but with potential applications in LMICs worldwide Haniffa et al. developed three models for ICU mortality prediction: model 1 with clinical, laboratory, and treatment variables; model 2 with clinical and laboratory variables; and model 3, a purely clinical model. Internal validation based on bootstrapping (1000 samples) was used to calculate discrimination (area under the receiver operating characteristic curve (AUC)) and calibration (Hosmer-Lemeshow C-Statistic; higher values indicate poorer calibration). Comparison was made with the Acute Physiology and Chronic Health Evaluation (APACHE) II and Simplified Acute Physiology Score (SAPS) II models [50]. Models 1 and 2 turned out to be superior to APACHE II, SAPS II, and model 3, The authors propose the acronym TropICS (Tropical Intensive Care Score) for model 2 as the first multinational critical care prognostic model developed in a non-HIC setting, whose superior overall performance, simplicity, and objectivity may enable prospective assessment in resource-limited settings in Asia, Africa, and South America to determine generalizability.

Kuteesa et al. in their prospective observational study conducted from January to April 2015 among 192 patients undergoing emergency laparotomy discovered that patients with intraabdominal hypertension (IAH) preoperatively were 2.7 times more likely to develop respiratory dysfunction compared to those without IAH and that patients with IAH postoperatively at 6 h and at 24 h were noted to be more than 2.933 and 3.769 times more likely to die than those without IAH [78]. The mortality associated with IAH postoperatively at 6 and 24 h shows the need to objectively measure IAP in patients at risk, for early recognition and effective intervention,

based on clinical protocols, designed to guide the management of patients with IAH in the accidents and emergency surgery wards. Resources should also be channeled towards procurement of equipment required to monitor the IAP in these patients.

In their systematic review of the medical literature Hoyler et al. studied whether the task-shifting or the redistribution of responsibilities from fully trained surgeons to clinicians with fewer qualifications could become a major component of surgical care delivery in many low-income and middle-income countries (LMICs) [79]. They identified 65 articles and 14 abstracts that described non-surgeon and non-physician providers performing 46 types of surgical procedures, beyond those recommended by WHO, across eight surgical disciplines, in 41 LMICs, non-surgeons and non-physicians provided a large amount of surgical care in some locations, including 90% of obstetric surgeries, 38.5% of general surgery procedures, and 43% of non-obstetric laparotomies at three separate hospitals.

As an example of regional initiative, The Cartagena declaration for trauma and injuries data collection in Latin America stating that trauma is a public health problem in Latin America with substantial social and economic impact due to its high mortality rate and associated physical and mental disability, representing a significant percentage of national healthcare spending in the region, appeals for combining efforts of Ministries of Health, academic bodies, and scientific societies to develop long-term policies to sustain and improve national and international trauma data collection systems and create robust partnerships for change, across countries so gravely affected by this epidemic [80].

In mass casualty incidents (MCIs) the efficiency of triage is particularly important for managing casualties when resources are limited [81]. Inappropriate triage protocols may lead to catastrophic consequences, such as misusing valuable resources on overtriaged patients and jeopardizing undertriaged ones [82].

Estimating the triage accuracy and ability to predict ED disposition of Simple triage and rapid treatment (START) and Taiwan Triage and Acuity Scale (TTAS) of 105 victims following an earthquake-related MCI, Lin et al. observed similar capacity, with START allowing shorter triage times compared with TTAS [83]. The authors suggest that START is an alternative to TTAS for the ED triage of victims of earthquake-related MCIs.

Caring for critically ill patients in resource-limited settings is challenging due to the high burden of disease and high mortality rates from potentially treatable critical illnesses [71]. Potential solutions for the improvement of care for critically ill patients in resource-poor settings can include a set of priorities like:

- consideration of safe, equitable, and high-quality critical care in resource-limited settings as a must for international health security
- defining critical care activities, education, training, and research as national priorities
- outlining in public health the burden of critical care disease access, diagnosis and management as priority issue with substantial impact on global health, focusing on quality improvement, and cost-effectiveness.

The alarming results of WSES COVID-19 emergency surgery survey show a combination of decrease in numbers of emergency surgical patients and increase in more severe septic diseases may be as a result of the fear of patients from infection with COVID-19 and a consecutive delayed hospital admission and diagnosis [84]. A critical delay in time-to-diagnosis and time-to-intervention as a possible result of changes in in-hospital logistics and operating room as well as intensive care capacities may reflect the potentially harmful impact of SARS-CoV-2 pandemic on emergency surgery services.

18.6 Future Prospective for Management of MOF in Low-Resource Settings: Changing Policies, Application of Rational Strategies, Optimizing Resources

The burden of critical illness in low-income and middle-income countries (LMICs) is substantial.

A better understanding of critical care outcomes is essential for improving critical care delivery in resource-limited settings [35].

Further research is warranted to develop real-time assessment techniques for microcirculation and evaluate the effects of therapeutic interventions to achieve optimal management of critically ill patients. In addition, prospective studies are needed to identify robust molecular targets considering disease heterogeneity. These targets, in combination with novel therapeutic interventions, will guide the accurate diagnosis and management of sepsis, SIRS, and MOF [29].

Addressing both disease-specific and setting-specific factors is important to improve performance of ICUs in LMICs. Although critical care for severe sepsis is likely cost-effective in LMIC setting, more detailed evaluation at both at a macro- and micro-economy level is necessary. Sepsis management in resource-limited settings is a largely unexplored frontier with important opportunities for research, training, and other initiatives for improvement [23].

Surgical providers often had no formal *surgical training* and did not operate under the supervision of a fully trained provider. It was obvious that many non-surgeon physicians and non-physician clinicians provide surgical care in low-resource settings. In view of the shortage of fully trained surgeons in many LMICs, it seems likely that task-shifting is far more widespread than is indicated by the medical literature. More research is needed to accurately determine the full extent and implications of surgical task-shifting in LMICs worldwide [79].

In their cross sectional study, using an anonymous online, questionnaire of 175 ICQ personnel from LMICs and 43 from HICs Haniffa et al. found out that LMICs ICU workers perceived lack of training, lack of nurses, and low wages as major barriers to functioning [85]. Training, increase of nurse workforce, and collection of outcome data were proposed as useful strategies to improve LMIC ICU services.

Innovation, surgical challenges like laparoscopic surgery may be safe, effective, feasible, and cost-effective in LMICs, although it often remains limited in its

accessibility, acceptability, and quality. Surgeons, policymakers, and manufacturers should focus on plans for sustainability, training, and retention of providers, and regulation of efforts to develop laparoscopy in LMICs [86].

Optimal surgical performance is highly complex and requires providers to integrate and communicate information regarding the patient, task, team, and environment to coordinate team-based care that is timely, effective, and safe. Resource limitations common to many LMICs present unique challenges to surgeons operating in these environments, but have never been formally described [87]. Resource variability rather than lack of resources underlies many contextual challenges to safe surgical care in a LMIC setting. Understanding these challenges and resilient strategies to overcome them is critical for both LMIC surgical providers and surgeons from HICs working in similar settings.

Outcomes from HICs cannot be reliably extrapolated to LMICs, so it is important to analyze outcomes for critically ill patients in LMICs. Specific challenges to achieving meaningful outcomes studies in LMICs include defining the critically ill population when few ICU beds exist, the resource-intensiveness of long-term follow-up, and the need for reliable severity of illness scores to interpret outcomes. Although much work remains to be done, examples of studies overcoming these challenges are beginning to emerge [35].

Multicenter studies are needed to validate qSOFA and the UVA score and variations thereof as suggested, in various settings, and assess whether the use of these scores can improve patient outcomes in resource-limited settings by rapid diagnosis and intervention for sepsis and its complications [52].

Future quality improvement studies would benefit from collaboration among multiple centers to improve generalizability and from adaptation of scores appropriate for resource-constrained settings [43].

More studies are needed to demonstrate proper guidelines on monitoring of IAP in patients undergoing emergency laparotomy [78].

The applicability and uptake of prognostic models in LMICs is poorly explored, due to limited availability of studies validating model performance and high degree of missing information Existing models are infrequently used by clinicians, administrators, and decision makers in these settings, probably reflecting their perceived lack of relevance to the patient population and, in part, due to the lack of feasibility of data collection [50].

The care of the surgical patients in an intensive care setting in countries with resource limitations should be optimized, protocols for standardized care—implemented and better research and resource allocation, as well as investment in healthcare training are essential for the development of intensive care in LMICs is necessary [36].

Health care professionals from resource-rich and resource-limited settings should take a global perspective on critical care for both ethical and practical reasons Ethically, health care professionals, trainees, professional societies, nongovernmental organizations (NGOs), and international organizations from resource-rich settings have the capacity of deploying resources to improve outcomes for critically ill patients in resource-limited settings Assistance can include financial

help, knowledge exchange in the form of research and educational partnerships, and capacity building in operations and implementation science. Supporting resource-limited settings is very important, because economic consequences of pandemics and conflicts driving mass migration can reach far beyond local borders [71].

Further measures are necessary to reduce time-to-diagnosis and time-to-intervention in emergency departments around the world, to prevent medical staff and patients from infection with COVID-19, and to protect infected patients from a perioperative exacerbation of the disease with consecutive severe morbidities and mortality and prevent the need for triage of emergency surgical patients and provide a timely surgical therapy in all (infected or non-infected) urgent and emergency patients. The WSES supports all efforts to fight for an optimized treatment of our surgical emergency patients both in cases of local COVID-19 outbreak and also the worldwide setting [84].

Following the WHO prospective, multi-center, multi-country studies including the AFRINEST (African Neonatal Sepsis Trial), SATT (Simplified Antibiotic Therapy Trial), GLOSS (Global Maternal Sepsis Study), MCS-A (Multi-Country Survey on Abortion) concerning neonate and maternal sepsis death, the surgical and critical care physician academics should perform similar studies, investigating MODS and MOF lethal factors in low-resource setting to fight against its unacceptably high death rate.

18.7 Home Messages

1. MOF is difficult to treat, escalates quickly, and is often fatal, for which early detection is crucial in preventing its progression especially in LMICs, where low resources and qualification is limited.
2. Remodeled strategies and local conditions adapted assessment tools and therapies are the key activities to save more lifes in patients with Multiple Organ Dysfunction Syndrome in LMICs.
3. MOF is a serious condition and can be life-threatening in LMICs if not addressed early. MOF patients in low-resource settings require urgent escalation of care and support of the affected organs.

References

1. Murthy S, Adhikari NK. Global health care of the critically ill in low resource settings. Ann Am Thorac Soc. 2013;10:509–13.
2. Vincent JL, Marshall JC, Namendys-Silva SA, et al. ICON investigators. Assessment of the worldwide burden of critical illness: the Intensive Care Over Nations (ICON) audit. Lancet Respir Med. 2014;2:380–6.
3. Dunser M, Baelani WI, Ganbold L. A review and analysis of intensive care medicine in the least developed countries. Crit Care Med. 2006;34:1234–42.

4. Adhikari N, Fowler R, Bhagwanjee S, Rubenfeld G. Critical care and the global burden of critical illness in adults. Lancet. 2010;376:1339–46.
5. Fowler R, Adhikari N, Bhagwanjee S. Clinical review: critical care in the global context – disparities in burden of illness, access, and economics. Crit Care. 2008;12(225):1–6.
6. Al-Khafaji A. Multiple organ dysfunction syndrome in sepsis. Medscape; 2020. https://emedicine.medscape.com/article/169640-ovsystemirview.
7. Murray C, Lopez A. Measuring the global burden of disease. N Engl J Med. 2013;369:448–57.
8. Annez P, Linn J. An agenda for research on urbanization in developing countries: a summary of findings from a scoping exercise. Geneva: The World Bank; 2010.
9. World Health Organization Ebola Response Team. Ebola virus disease in West Africa—the first 9 months of the epidemic and forward projections. N Engl J Med. 2014;371:1481–95.
10. Stafford R, Morrison C, Godfrey G, Mahalu W. Challenges to the provision of emergency services and critical care in resource-constrained settings. Glob Heart. 2014;9(3):319–23.
11. Procter L. 2019. Shock. MSD manual; 2020. https://www.msdmanuals.com/home/heart-and-blood-vessel-disorders/low-blood-pressure-and-shock/shock.
12. Osterbur K, Mann FA, Kuroki K, DeClue A. Multiple organ dysfunction syndrome in humans and animals. J Vet Intern Med. 2014;28(4):1141–51.
13. Nickson C. Multiple organ dysfunction syndrome. Life in the Fastlane; 2019. https://litfl.com/multiple-organ-dysfunction-syndrome.
14. WHO. Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions. Geneva: World Health Organization; 2020. ISBN978-92-4-001078-9.
15. Gu C, Qiao W, Wang L, Li M, Song K. Identification of genes and pathways associated with multiple organ dysfunction syndrome by microarray analysis. Mol Med Rep. 2018;18(1):31. https://www.spandidos-publications.com/10.3892/mmr.2018.8973
16. Harper SJF, Saeb-Parsy K. Essential surgery e-book: problems, diagnosis and management. Amsterdam: Elsevier Health Sciences; 2013. https://books.google.com.au/books?id=RYhRAAAAQBAJ&dq=mods+unregulated+immune+response&source=gbs_navlinks_s
17. Rossaint J, Zarbock A. Pathogenesis of multiple organ failure in sepsis. Crit Rev Immunol. 2015;35:4. https://pubmed.ncbi.nlm.nih.gov/26757392/
18. Carrico CJ, Meakins JL, Marshall JC, Fry D, Maier RV. Multiple-organ-failure syndrome. Arch Surg. 1986;121(2):196–208.
19. Sauaia A, Moore E, Johnson J, Ciesla D, Biffl W, Banerjee A. Validation of postinjury multiple organ failure scores. Shock. 2009;31(5):438–47.
20. Dharap S, Ekhande S. An observational study of incidence, risk factors & outcome of systemic inflammatory response & organ dysfunction following major trauma. Indian J Med Res. 2017;146(3):346–53.
21. Wang Z, et al. Clinical application of a novel diagnostic scheme including pancreatic β-cell dysfunction for traumatic multiple organ dysfunction syndrome. Mol Med Rep. 2018;17(1):683. https://www.spandidos-publications.com/10.3892/mmr.2017.7898.
22. Harjola V, et al. Organ dysfunction, 'injury and failure in acute heart failure: from pathophysiology to diagnosis and management. a review on behalf of the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC)'. Eur J Heart Fail. 2017;19(7):821.
23. Schultz M, Dunser M, Dondorp A, et al. Global Intensive Care Working Group of the European Society of Intensive Care Medicine. Current challenges in the management of sepsis in ICUs in resource-poor settings and suggestions for the future. Intensive Care Med. 2017;43(5):612–24.
24. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10.
25. Fleischmann C, Scherag A, Adhikari NKJ, et al. International Forum of Acute Care Trialists. Assessment of global incidence and mortality of hospital-treated sepsis: current estimates and limitations. Am J Respir Crit Care Med. 2016;193(3):259–72.
26. Gosselin R, Spiegel DA, Coughlin R, Zirkle LG. Injuries: the neglected burden in developing countries. Bull WHO. 2009;87(4):246–246a.

27. Mathers C, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3(11):e442.
28. Mock C, Kobusingye O, Joshipura M, et al. Strengthening trauma and critical care globally. Curr Opin Crit Care. 2005;11(6):568–75.
29. Asim M, Amin F, El-Menyar A. Multiple organ dysfunction syndrome: contemporary insights on the clinicopathological spectrum. Qatar Med J. 2020;2020(1):22. https://doi.org/10.5339/qmj.2020.22.
30. Ilori IU, Kalu QN. Intensive care admissions and outcome at the University of Calabar Teaching Hospital, Nigeria. J Crit Care. 2012;27:105.e1–4.
31. Smith ZA, Ayele Y, McDonald P. Outcomes in critical care delivery at Jimma University Specialised Hospital. Ethiopia Anaesth Intens Care. 2013;41:363–8.
32. Kwizera A, Dьnser M, Nakibuuka J. National intensive care unit bed capacity and ICU patient characteristics in a low income country. BMC Res Notes. 2012;5:475.
33. Baker T, Blixt J, Lugazia E, et al. Single deranged physiologic parameters are associated with mortality in a low-income country. Crit Care Med. 2015;43:2171–9.
34. Lobo SM, Rezende E, Knibel MF, et al. Early determinants of death due to multiple organ failure after noncardiac surgery in high-risk patients. Anesth Analg. 2011;112(4):877–83.
35. Vukoja M, Riviello ED, Schultz MJ. Critical care outcomes in resource-limited settings. Curr Opin Crit Care. 2018;24(5):421–7.
36. Ribeiro MAF Jr, Fonseca AZ, Santin S. Caring for the surgical patient with limited ICU resources. Curr Opin Crit Care. 2019;25(6):697–700.
37. Murthy S, Leligdowicz A, Adhikari NK. Intensive care unit capacity in low-income countries: a systematic review. PLoS One. 2015;10(1):e0116949.
38. Fleischmann-Struzek C, Mellhammar L, Rose N, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. Intensive Care Med. 2020;46:1552–62.
39. Rahman M, Shad F, Smith MC. Acute kidney injury: a guide to diagnosis and management. Am Fam Physician. 2012;86(7):631. https://www.aafp.org/afp/2012/1001/p631.html/.
40. Washmuth D. Multi-organ dysfunction syndrome: causes, diagnosis & management. Study.com; 2017. https://study.com/academy/lesson/multi-organ-dysfunction-syndrome-causes-diagnosis-management.html.
41. Adhikari NK, Fowler RA, Bhagwanjee S, et al. Critical care and the global burden of critical illness in adults. Lancet. 2010;376:1339–46.
42. Stafford RE, Morrison CA, Godfrey G, et al. Challenges to the provision of emergency services and critical care in resource-constrained settings. Glob Heart. 2014;9:319–23.
43. Parker R, Mwachiro E, Mwachiro M, et al. Mortality prediction in rural Kenya: a cohort study of mechanical ventilation in critically ill patients. Crit Care Explor. 2019;1(12):e0067.
44. Aluisio AR, Garbern S, Wiskel T, et al. Mortality outcomes based on ED qSOFA score and HIV status in a developing low income country. Am J Emerg Med. 2018;36:2010–9.
45. Khwannimit B, Bhurayanontachai R, Vattanavanit V. Comparison of the performance of SOFA, qSOFA and SIRS for predicting mortality and organ failure among sepsis patients admitted to the intensive care unit in a middle-income country. J Crit Care. 2018;44:156–60.
46. Beane A, De Silva AP, De Silva N, et al. Evaluation of the feasibility and performance of early warning scores to identify patients at risk of adverse outcomes in a low-middle income country setting. BMJ Open. 2018;8:e019387.
47. Moore C, Hazard R, Saulters K, et al. Derivation and validation of a universal vital assessment (UVA) score: a tool for predicting mortality in adult hospitalised patients in sub-Saharan Africa. BMJ Glob Health. 2017;2:e000344.
48. Baker T, Schell C, Lugazia E, et al. Vital signs directed therapy: improving care in an intensive care unit in a low-income country. PLoS One. 2015;10:e0144801.
49. Rudd K, Seymour C, Aluisio A, et al. Association of the quick sequential (sepsis-related) organ failure assessment (qSOFA) score with excess hospital mortality in adults with suspected infection in low- and middle-income countries. JAMA. 2018;319:2202–11.

50. Haniffa R, Mukaka M, Munasinghe SB, et al. Simplified prognostic model for critically ill patients in resource limited settings in South Asia. Crit Care. 2017;21:250.
51. Riviello ED, Kiviri W, Fowler RA, et al. Predicting mortality in low-income country ICUs: the Rwanda mortality probability model (R-MPM). PLoS One. 2016;11:e0155858.
52. Schmedding M, Adegbite B, Gould S, et al. A prospective comparison of quick sequential organ failure assessment, systemic inflammatory response syndrome criteria, universal vital assessment, and modified early warning score to predict mortality in patients with suspected infection in Gabon. Am J Trop Med Hyg. 2019;100:202–8.
53. Machado FR, Cavalcanti AB, Monteiro MB, et al. Predictive accuracy of the quick sepsis-related organ failure assessment score in Brazil. A prospective multicenter study. Am J Respir Crit Care Med. 2020;20:789–98.
54. Klinger A, Mueller A, Sutherland T, et al. Predicting mortality in adults with suspected infection in a Rwandan hospital: an evaluation of the adapted MEWS, qSOFA and UVA scores. BMJ Open. 2021;11:e040361. https://doi.org/10.1136/bmjopen-2020-040361.
55. Sinto R, Suwarto S, Lie KC, et al. Prognostic accuracy of the quick Sequential Organ Failure Assessment (qSOFA)-lactate criteria for mortality in adults with suspected bacterial infection in the emergency department of a hospital with limited resources. Emerg Med J. 2020;37:363–9.
56. Song J, Sin C, Park H, Shim S, Lee J. Performance of the quick sequential (sepsis-related) organ failure assessment score as a prognostic tool in infected patients outside the intensive care unit: a systematic review and meta-analysis. Crit Care. 2018;22:28.
57. Fernando S, Tran A, Taljaard M, et al. Prognostic accuracy of the quick sequential organ failure assessment for mortality in patients with suspected infection: a systematic review and meta-analysis. Ann Intern Med. 2018;168:266–75.
58. Serafim R, Gomes J, Salluh J, Povoa P. A comparison of the quick-SOFA and systemic inflammatory response syndrome criteria for the diagnosis of sepsis and prediction of mortality: a systematic review and meta-analysis. Chest. 2018;153:646–55.
59. Maitra S, Som A, Bhattacharjee S. Accuracy of quick sequential organ failure assessment (qSOFA) score and systemic inflammatory response syndrome (SIRS) criteria for predicting mortality in hospitalized patients with suspected infection: a meta-analysis of observational studies. Clin Microbiol Infect. 2018;24:1123–9.
60. Baig MA, Sheikh S, Hussain E, et al. Comparison of qSOFA and SOFA score for predicting mortality in severe sepsis and septic shock patients in the emergency department of a low middle income country. Turk J Emerg Med. 2018;18(4):148–51.
61. Sendagire C, Lipnick MS, Kizito S, et al. Feasibility of the modified sequential organ function assessment score in a resource-constrained setting: a prospective observational study. BMC Anesthesiol. 2017;17(1):12.
62. Lukoko LN, Kussin PS, Adam RD, Orwa J, Waweru-Siika W. Investigating SOFA, delta-SOFA and MPM-III for mortality prediction among critically ill patients at a private tertiary hospital ICU in Kenya: a retrospective cohort study. PLoS One. 2020;15(7):e0235809.
63. Kruisselbrink R, Kwizera A, Crowther M, et al. Modified Early Warning Score (MEWS) Identifies critical illness among ward patients in a resource restricted setting in Kampala, Uganda: a prospective observational study. PLoS One. 2016;11(3):e0151408.
64. Salluh JI, Soares M. ICU severity of illness scores: APACHE, SAPS and MPM. Curr Opin Crit Care. 2014;20:557–65.
65. Granholm A, Perner A, Krag M, et al. Development and internal validation of the simplified mortality score for the intensive care unit (SMSICU). Acta Anaesthesiol Scand. 2018;62:336–46.
66. Lalani HS, Waweru-Siika W, Mwogi T, et al. Intensive care outcomes and mortality prediction at a National Referral Hospital in Western Kenya. Ann Am Thorac Soc. 2018;15(11):1336–43. https://doi.org/10.1513/AnnalsATS.201801-051OC.
67. Singer M. Management of multiple organ failure: guidelines but no hard-and-fast rules. J Antimicrob Chemother. 1998;41(Suppl A):103–12.

68. Chapalain X, Vermeersch V, Egreteau PY, et al. Association between fluid overload and SOFA score kinetics in septic shock patients: a retrospective multicenter study. J Intensive Care. 2019;7:42.
69. Scala R, Pisani L. Noninvasive ventilation in acute respiratory failure: which recipe for success? Eur Respir Rev. 2018;27(149):180029.
70. Gourd N, Nikitas N. Multiple organ dysfunction syndrome. J Intensive Care Med. 2020;35(12):1564–75.
71. Diaz JV, Riviello ED, Papali A, Adhikari NKJ, Ferreira JC. Global critical care: moving forward in resource-limited settings. Ann Glob Health. 2019;85(1):3.
72. Kwizera A, Festic E, Dünser MW. What's new in sepsis recognition in resource-limited settings? Intensive Care Med. 2016;42(12):2030–3.
73. Serpa Neto A, Schultz M, Festic E. Ventilatory support of patients with sepsis or septic shock in resource-limited settings. Intensive Care Med. 2016;42(1):100–3.
74. Musa N, Murthy S, Kissoon N. Pediatric sepsis and septic shock management in resource-limited settings. Intensive Care Med. 2016;42(12):2037–9.
75. Dünser M, Festic E, Dondorp A, et al. Recommendations for sepsis management in resource-limited settings. Intensive Care Med. 2012;38(4):557–74.
76. Gianola S, Castellini G, Biffi A, et al. Accuracy of pre-hospital triage tools for major trauma: a systematic review with meta-analysis and net clinical benefit. World J Emerg Surg. 2021;16:31.
77. De Simone B, Chouillard E, Sartelli M, et al. The management of surgical patients in the emergency setting during COVID-19 pandemic: the WSES position paper. World J Emerg Surg. 2021;16:14.
78. Kuteesa J, Kituuka O, Namuguzi D, et al. Intra-abdominal hypertension; prevalence, incidence and outcomes in a low resource setting; a prospective observational study. World J Emerg Surg. 2015;10:57.
79. Hoyler M, Hagander L, Gillies R, Riviello R, Chu K, Bergström S, Meara JG. Surgical care by non-surgeons in low-income and middle-income countries: a systematic review. Lancet. 2015;385(Suppl 2):S42.
80. Dasari M, Johnson ED, Montenegro JH, et al. A consensus statement for trauma surgery capacity building in Latin America. World J Emerg Surg. 2021;16:4.
81. Bazyar J, Farrokhi M, Khankeh H. Triage systems in mass casualty incidents and disasters: a review study with a worldwide approach. Open Access Maced J Med Sci. 2019;7:482–94.
82. Zachariasse J, van der Hagen V, Seiger N, et al. Performance of triage systems in emergency care: a systematic review and meta-analysis. BMJ Open. 2019;9:e026471.
83. Lin YK, Niu KY, Seak CJ, et al. Comparison between simple triage and rapid treatment and Taiwan Triage and Acuity Scale for the emergency department triage of victims following an earthquake-related mass casualty incident: a retrospective cohort study. World J Emerg Surg. 2020;15:20.
84. Reichert M, Sartelli M, Weigand M, et al. Impact of the SARS-CoV-2 pandemic on emergency surgery services—a multi-national survey among WSES members. World J Emerg Surg. 2020;15:64.
85. Haniffa R, Pubudu De Silva A, de Azevedo L, et al. Improving ICU services in resource-limited settings: perceptions of ICU workers from low-middle-, and high-income countries. J Crit Care. 2018;44:352–6.
86. Chao TE, Mandigo M, Opoku-Anane J, Maine R. Systematic review of laparoscopic surgery in low- and middle-income countries: benefits, challenges, and strategies. Surg Endosc. 2016;30(1):1–10. https://doi.org/10.1007/s00464-015-4201-2.
87. Scott J, Lin Y, Ntakiyiruta G, et al. Contextual challenges to safe surgery in a resource-limited setting: a multicenter, multiprofessional qualitative study. Ann Surg. 2018;267(3):461–7.

19 Randomized Controlled Trials Affecting Postinjury Multiple-Organ Failure and Associated Prevention and Treatment

Dias Argandykov and George C. Velmahos

19.1 Introduction

Globally, injuries—both unintentional and violence-related—claim the lives of 4.4 million people, accounting for roughly 8% of all deaths [1]. In the USA, trauma continues to be the leading cause of death in the group of people aged 1–44 years old. As more patients survive the early trauma/resuscitation phase due to advancements in trauma care, postinjury multiple-organ failure (MOF) is becoming a daily consideration for critical care physicians, largely defining clinical outcomes. As expected, MOF has been associated with substantial healthcare resource utilization [2, 3]. These significant challenges necessitate a multidisciplinary approach involving trauma surgeons, anesthesiologists, critical care specialist, and multiple other experts working cohesively.

The current theory related to MOF suggests that acute physiologic insults result in two opposite but simultaneous responses: a pro-inflammatory one, the systemic inflammation response syndrome (SIRS), and an anti-inflammatory one, the systemic anti-inflammatory response syndrome (SARS, previously termed as compensatory (CARS)) [4]. The simultaneous occurrence of these counteracting immune responses was demonstrated in the Glue Grant study [5]. Therefore, treatment and prevention of post-insult MOF primarily depend on the efforts to attenuate systemic excessive immune activation while amplifying natural immunity.

As advances in immediate trauma care enabled a greater number of severely injured people to survive the immediate phase of trauma, postinjury MOF appeared as the major cause of late death. It is estimated that one-third of patients diagnosed with MOF die, typically shortly after diagnosis, indicating how short is the therapeutic window and how important is the prevention of MOF. The majority of

D. Argandykov · G. C. Velmahos (✉)
Division of Trauma, Emergency Surgery, and Surgical Critical Care, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
e-mail: gvelmahos@partners.org

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_19

severely injured patients who survive the first 24–48 h bear a relatively positive prognosis [6, 7]. Past the acute period following injury, initially sustained injuries represent a cause of death to a lesser extent. In contrast, infectious and septic complications arising as a result of imbalanced immune response account for the subsequent development of MOF and mortality [8]. Therefore, RCTs focus on modulating the balance between harmful immunological reactions leading to SIRS and beneficial innate immunity [9].

The goal of this review is to examine randomized controlled trials (RCTs) related to MOF. We primarily focus on the "second" stage of injury, during which the immediate threat of death has been prevented but the risk of MOF is still high. However, given the close correlation between early interventions and late complications, we also consider several major RCTs exploring hemorrhage control and initial resuscitation.

19.2 Judicious Use of Blood Transfusions

Major traumatic injuries are frequently associated with significant hemorrhage requiring massive blood transfusion. Earlier infusion of blood and blood products counters intravascular depletion and prevents trauma-induced coagulopathy. However, while red blood cell (RBC) transfusion is a life-saving strategy in selected patients with exsanguination, liberal transfusions to simply reconstitute laboratory values to arbitrary norms bear a significant risk of delayed complications, such as sepsis, MOF, and even death [10, 11]. Clearly, blood transfusion is one of the major independent risk factors for postinjury MOF [2, 3].

The replacement of crystalloid resuscitation with blood and blood product transfusion—or even better, whole blood—has emerged as a crucial strategy in modern resuscitation techniques [12, 13]. In a widely cited RCT by Holcomb et al., 680 severely injured patients who were expected to require massive transfusion were randomized to administration of plasma, platelets, and red blood cells in a 1:1:1 ratio vs. 1:1:2 ratio [14]. Among the two groups there were no significant differences in mortality at 24 h or at 30 days with more patients in the 1:1:1 group achieving hemostasis and fewer experiencing death due to exsanguination by 24 h. Again, the overall mortality was not different, nor were the incidences of ARDS, MOF, venous thromboembolism, and sepsis between the two treatment groups.

In another major RCT challenging the widely used prehospital resuscitation approaches, 230 injured patients, who were at risk for hemorrhagic shock, received plasma in comparison to a group of 271 patients, who received standard resuscitation [15]. Those resuscitated with plasma had a lower 30-day mortality (23.2% vs. 33.0%; 95% confidence interval (CI), −18.6 to −1.0; $p = 0.03$) and a lower median prothrombin-time ratio (1.2 vs. 1.3, $p < 0.001$) compared to the standard resuscitation patients. The plasma group did not have a higher incidence of inflammatory-mediated complications, such as MOF, ARDS, or nosocomial infections.

19.3 Prehospital Care and Protective Resuscitation Techniques

Following the immediate phase of trauma, the optimal choice of fluid volume replacement that might attenuate the late development of organ dysfunction has remained widely debated. In the late 1960s, despite the reduction of mortality and renal failure the administration of isotonic crystalloids contributed to the development of ARDS [16]. The controversy related to the use of crystalloids continued to be relevant in the context of comparison to colloids. In 2004 the multicenter SAFE trial did not demonstrate a significant difference in mortality in patients admitted to the ICU receiving 4% albumin vs. 0.9% saline [17].

Rizoli et al. in the first human RCT confirmed the immunologic/anti-inflammatory role of hypertonic saline in the resuscitation of trauma patients, suggesting a protective effect against postinjury MOF [18]. However, in a subsequent RCT Bulger et al. reported no significant changes in mortality between patients who received 7.5% hypertonic saline and those with 0.9% saline during the initial prehospital resuscitation phase [19]. Similarly, there was no significant difference in the rates of MOF or ARDS. A recent 2018 Cochrane systematic review of 69 studies including 30,020 critically ill patients identified no difference in mortality among patients receiving colloids (including starches; dextran; or albumin or fresh frozen plasma) and patients receiving crystalloids for fluid resuscitation [20].

It is important to consider that, while immediate and aggressive fluid resuscitation may have a seemingly positive impact on vital signs, the overall effect on outcome is far less encouraging. Kasotakis et al. found that aggressive volume replacement with crystalloids resulted not only in prolonged time on the ventilator and overall ICU and hospital length but seems to be associated with a significant increase in late complications including acute lunge injure/ARDS and MOF [21].

19.4 Head Trauma

Traumatic brain injury (TBI) has been a leading cause of death and long-term disability associated with poor quality of life and high economic and social costs. The primary goal of TBI management focuses on supporting an adequate cerebral perfusion pressure (CPP) and providing tissue oxygenation. However, non-neurological complications following TBI are common and have an independent association with higher morbidity and mortality. The pathophysiology of how the traumatized brain leads to non-neurological manifestations is quite complex and involves the balancing effects of parasympathetic and sympathetic systems, immune dysregulation, and neuroinflammation [22].

Following the landmark CRASH-2 study that demonstrated the clinical benefits of tranexamic acid in reducing surgical bleeding and mortality in patients with posttraumatic extracranial bleeding, its use has become widely popular in patients

presenting with hemorrhagic shock [23]. In the subsequent major RCT, the CRASH-3 trial, collaborators demonstrated the safety and survival benefit of tranexamic acid used within 3-h of injury in patients with TBI (485 vs. 525 events, OR: 0.89 [95% CI: 0.80–1.00]) [24]. Rowell et al. conducted a significant RCT to further investigate whether tranexamic acid provides long-term beneficial effects on neurological outcomes in patients with moderate to severe TBI. Among these patients the use of tranexamic acid within 2 h of injury did not significantly improve neurologic outcomes at 6 months following injury. A favorable neurologic outcome determined as a Glasgow Outcome Scale-Extended score >4 occurred in 65% of patients in the tranexamic acid group and 62% of patients in the placebo group (difference, 3.5%; $p = 0.16$) [25].

19.5 Hypothermia in TBI

Therapeutic hypothermia has long been considered a practical approach in attenuating secondary brain injury following trauma. It has been hypothesized that prophylactic hypothermia improves outcomes in patients with TBI due to the attenuation of the subsequent neuroinflammatory and biochemical cascades [26]. It is important to distinguish this use of prophylactic hypothermia from late-rescue hypothermia aimed at reducing intracranial pressure which was found to be harmful [27].

An early meta-analysis found that therapeutic hypothermia following severe TBI was associated with lower mortality and improved long-term neurologic outcomes [28]. A later meta-analysis similarly showed a decreased mortality rate associated with therapeutic hypothermia [29]. However, in the multicenter RCT that included 511 patients with severe traumatic injury, Cooper et al. did not find a significant difference in 6-month neurological outcomes (GOS-E) while comparing the prophylactic hypothermia with normothermia (risk difference, 0.4% [95% CI, −9.4% to 8.7%]) [30]. There is still much clinical ambiguity about the long-term benefits of early prophylactic hypothermia.

19.6 Protective Lung Ventilation

Acute lung injury (ALI) is the precursor of ARDS and its related morbidity and mortality [31]. A landmark RCT by the Acute Respiratory Distress Syndrome Network demonstrated that mechanical ventilation with a lower tidal volume in patients with ALI and ARDS significantly contributed to decreased mortality and increased ventilator-free days [32]. Despite the complex pathophysiology of how mechanical ventilation further exacerbates lung injury, the results of clinical trials and a 2013 meta-analysis clearly demonstrate a survival benefit of lung-protective ventilation strategies [33, 34].

19.7 The Role of Corticosteroid Therapy

Trauma patients often experience a concomitant adrenal insufficiency [35]. The resulting corticosteroid insufficiency has been correlated with the development of prolonged SIRS which was in turn predictive of nosocomial infections in severely injured patients [36]. The posttraumatic hospital course of severely injured patients is frequently associated with the development of pneumonia, particularly among victims with traumatic brain injury, reaching rates of 40–60% [37]. Stress-dose hydrocortisone therapy has long been recommended as an important way to improve the mortality rate among the patients with septic shock and adrenal insufficiency [38]. Hydrocortisone is deemed to reduce the inflammatory response without suppressing the immune system, thus restoring a sufficient immunological response to infection [39] In addition, Roquilly et al. conducted an RCT that demonstrated a lower rate of hospital-acquired pneumonia at Day 28 in the group of patients who received stress-dose corticosteroid therapy compared to placebo (hazard ratio [HR] = 0.51; 95% confidence interval [CI] = 0.30–0.83; $p = 0.007$) [40]. In addition, trauma patients exposed to stress-dose hydrocortisone had more ventilator-free days by 4 days (95% CI, 2–7; $p = 0.001$) and decreased length of ICU stay (−6 days, 95% CI, −11 to −1; $p = 0.03$).

19.8 Insulin and Tight Glucose Control

Trauma-induced hyperglycemia has been considered a secondary response to elevated levels of glucagon, epinephrine, and cortisol stimulating gluconeogenesis [41]. In the landmark RCT done by van den Berghe et al. examining the role of intensive insulin therapy (IIT), a glucose level at or below 110 mg/dL was associated with reduced 12-month mortality rate among 1548 surgical ICU patients [42]. Importantly, the most significant reduction in mortality was related to a greater decrease in deaths due to multiple-organ failure. However, the results of a large, multicenter RCT conducted by the NICE-SUGAR Study investigators showed that intensive glucose control increased mortality in critically ill patients fueling further controversy [43].

A meta-analysis of seven RCTs studying the impact of intensive insulin therapy involved 11,425 ICU patients and revealed no evidence of decreased mortality, bloodstream infection rate, and the requirement for renal replacement therapy associated with tight glycemic control [44]. A more recent meta-analysis across ten RCTs involving 1011 patients with TBI similarly showed no difference in mortality rates [45]. Interestingly, tight glucose control similarly did not show significant effect on major clinical outcome in critically ill pediatric population [46]. Despite the absence of a universal consensus as to whether tighter glucose control (81–108 mg/dL) in critical care patients is associated with improved health

outcomes, intensive insulin therapy has been suggested as standard of care [47]. It was proposed that besides glucose homeostasis, insulin can diminish SIRS and modulate cellular and immune responses associated with severe trauma [48].

19.9 Immunonutrition

There has been a great interest in the assessment of enteral therapies on the clinical outcome of critically ill patients. Besides the primary goal of meeting the caloric requirements, nutritional therapy elicits a complex immunologic response that may not only improve the shock-induced bowel hypoperfusion but also attenuate gut permeability defects and decrease the severity of CARS [4]. Enteral nutrition (EN) has been preferred over parenteral nutrition (PN) in severely injured patients undergoing surgery, especially when started early. One of the first RCTs comparing EN vs. PN demonstrated a lower rate of pneumonia and fewer intra-abdominal abscesses and central line associated bloodstream infections among EN patients. Since then, in a variety of surgical ICU patients EN has shown to be superior to PN. In contrast to the above research, a recent RCT failed to find a statistically significant reduction in mortality and secondary infections in critically ill patients with shock and mechanical ventilation, who received EN or PN [49]. Exploring the issue of timing of nutrition, another RCT concluded that late initiation of PN (after Day 8) was associated with faster recovery (hazard ratio, 1.06; CI, 1.00–1.13; $p = 0.04$) and less ICU infections (22.8% vs. 26.2%, $p = 0.008$) in comparison to early initiation of PN (within 48 h after ICU admission) [50]. Nevertheless, the 90-day mortality rate was similar between the two groups. When compared to pragmatic standards of care, Doig et al. found no benefit of early PN in 60-day mortality [51]. Similarly, in a meta-analysis examining 24 RCTs, seven of which assessed the effects of immunonutrition in trauma patients, no significant effect on mortality (OR 1.03; 95% CI 0.40–2.65) and infection rate (OR 0.72; 95% CI 0.27–1.91) was identified when compared to standard diets [52].

With regard to immunonutrition in critically ill patients, a number of products have been investigated including amino acids, nucleotides, fish oils, glucans, and probiotics. The main goal of immunonutrition is to restore the functional response of the immune system by regulating cellular defense, oxidative stress, and mitochondrial function [9]. Nevertheless, the findings of these approaches remain inconclusive and controversial. One multicenter RCT assessing the addition of omega-3 fatty acids, glutamine, and antioxidants as immune-modulating treatment in comparison to high-protein enteral nutrition in critically ill patients did not find any significant difference in the incidence of infections, mortality, and SOFA scores [53]. A meta-analysis examining five small RCTs (281 patients overall) showed that the use of probiotics was associated with a decreased incidence of nosocomial infections and ventilator-associated pneumonia among trauma patients [54]. However, a meta-analysis of RCTs examining larger cohorts of critically ill patients (not particularly trauma) did not provide compelling evidence in favor of immunonutrients [55]. Most of the suggested approaches based on nutritional therapy interventions following trauma have not showed improved mortality [33].

References

1. WHO. Injuries and violence; 2021. https://www.who.int/news-room/fact-sheets/detail/injuries-and-violence. Accessed 21 Jun 2021.
2. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A, Hoyt D, Margulies D, Pruitt B, Fry D, Jurkovich G, Asensio JA. A 12-year prospective study of postinjury multiple organ failure: has anything changed? Arch Surg. 2005;140(5):432–40. https://doi.org/10.1001/archsurg.140.5.432.
3. Sauaia A, Moore EE, Johnson JL, Chin TL, Banerjee A, Sperry JL, Maier RV, Burlew CC. Temporal trends of postinjury multiple-organ failure: still resource intensive, morbid, and lethal. J Trauma Acute Care Surg. 2014a;76(3):582–93. https://doi.org/10.1097/TA.0000000000000147.
4. Moore FA, Moore EE. The evolving rationale for early enteral nutrition based on paradigms of multiple organ failure: a personal journey. Nutr Clin Pract. 2009;24(3):297–304. https://doi.org/10.1177/0884533609336604.
5. Xiao W, Mindrinos MN, Seok J, Cuschieri J, Cuenca AG, Gao H, Hayden DL, Hennessy L, Moore EE, Minei JP, Bankey PE, Johnson JL, Sperry J, Nathens AB, Billiar TR, West MA, Brownstein BH, Mason PH, Baker HV, et al. A genomic storm in critically injured humans. J Exp Med. 2011;208(13):2581–90. https://doi.org/10.1084/jem.20111354.
6. Lefering R, Paffrath T, Bouamra O, Coats TJ, Woodford M, Jenks T, Wafaisade A, Nienaber U, Lecky F. Epidemiology of in-hospital trauma deaths. Eur J Trauma Emerg Surg. 2012;38(1):3–9. https://doi.org/10.1007/s00068-011-0168-4.
7. Oyeniyi BT, Fox EE, Scerbo M, Tomasek JS, Wade CE, Holcomb JB. Trends in 1029 trauma deaths at a level 1 trauma center: impact of a bleeding control bundle of care. Injury. 2017;48(1):5–12. https://doi.org/10.1016/j.injury.2016.10.037.
8. Prin M, Li G. Complications and in-hospital mortality in trauma patients treated in intensive care units in the United States, 2013. Injury Epidemiol. 2016;3(1):18. https://doi.org/10.1186/s40621-016-0084-5.
9. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, Moldawer LL, Moore FA. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. J Trauma Acute Care Surg. 2012;72(6):1491–501. https://doi.org/10.1097/TA.0b013e318256e000.
10. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med. 1999;340(6):409–17. https://doi.org/10.1056/nejm199902113400601.
11. Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. J Trauma. 2003;52(5):898–907. https://doi.org/10.1097/01.TA.0000060261.10597.5C.
12. Holcomb JB, Del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, Alarcon LH, Bai Y, Brasel KJ, Bulger EM, Cotton BA, Matijevic N, Muskat P, Myers JG, Phelan HA, White CE, Zhang J, Rahbar MH. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg. 2013;148(2):127–36. https://doi.org/10.1001/2013.jamasurg.387.
13. Holcomb JB, Wade CE, Michalek JE, Chisholm GB, Zarzabal LA, Schreiber MA, Gonzalez EA, Pomper GJ, Perkins JG, Spinella PC, Williams KL, Park MS. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg. 2008;248(3):447–56. https://doi.org/10.1097/SLA.0b013e318185a9ad.
14. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, Del Junco DJ, Brasel KJ, Bulger EM, Callcut RA, Cohen MJ, Cotton BA, Fabian TC, Inaba K, Kerby JD, Muskat P, O'Keeffe T, Rizoli S, Robinson BRH, Scalea TM, Schreiber MA, Stein DM, Weinberg JA, Callum JL, Hess JR, Matijevic N, Miller CN, Pittet JF, Hoyt DB, Pearson GD, Leroux B, van Belle G, PROPPR Study Group. 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. 2015;313(5):471–82. https://doi.org/10.1001/jama.2015.12.
15. Sperry JL, Guyette FX, Brown JB, Yazer MH, Triulzi DJ, Early-Young BJ, Adams PW, Daley BJ, Miller RS, Harbrecht BG, Claridge JA, Phelan HA, Witham WR, Putnam AT, Duane TM, Alarcon LH, Callaway CW, Zuckerbraun BS, Neal MD, et al. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. N Engl J Med. 2018;379(4):315–26. https://doi.org/10.1056/nejmoa1802345.
16. Sauaia A, Moore FA, Moore EE. Postinjury inflammation and organ dysfunction. Crit Care Clin. 2017;33(1):167–91. https://doi.org/10.1016/j.ccc.2016.08.006.
17. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Ch B, Norton R-B. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350(22):2247–56. https://doi.org/10.1056/nejmoa040232.
18. Rizoli SB, Rhind SG, Shek PN, Inaba K, Filips D, Tein H, Brenneman F, Rotstein O. The immunomodulatory effects of hypertonic saline resuscitation in patients sustaining traumatic hemorrhagic shock: a randomized, controlled, double-blinded trial. Ann Surg. 2006;243(1):47–57. https://doi.org/10.1097/01.sla.0000193608.93127.b1.
19. Bulger EM, May S, Kerby JD, Emerson S, Stiell IG, Schreiber MA, Brasel KJ, Tisherman SA, Coimbra R, Rizoli S, Minei JP, Hata JS, Sopko G, Evans DC, Hoyt DB. Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: a randomized, placebo controlled trial. Ann Surg. 2011;253(3):431–41. https://doi.org/10.1097/SLA.0b013e3181fcdb22.
20. Lewis SR, Pritchard MW, Evans DJW, Butler AR, Alderson P, Smith AF, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill people. Cochrane Database Syst Rev. 2018;(8):CD000567. https://doi.org/10.1002/14651858.CD000567.pub7.
21. Kasotakis G, Sideris A, Yang Y, De Moya M, Alam H, King DR, Tompkins R, Velmahos G. Aggressive early crystalloid resuscitation adversely affects outcomes in adult blunt trauma patients: an analysis of the Glue Grant database. J Trauma Acute Care Surg. 2013;74(5):1215–22. https://doi.org/10.1097/TA.0b013e3182826e13.
22. Simon DW, McGeachy MJ, Baylr H, Clark RSB, Loane DJ, Kochanek PM. The far-reaching scope of neuroinflammation after traumatic brain injury. Nat Rev Neurol. 2017;13(3):171–91. https://doi.org/10.1038/nrneurol.2017.13.
23. Olldashi F, Kerçi M, Zhurda T, Ruçi K, Banushi A, Traverso MS, Jiménez J, Balbi J, Dellera C, Svampa S, Quintana G, Piñero G, Teves J, Seppelt I, Mountain D, Hunter J, Balogh Z, Zaman M, Druwé P, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376(9734):23–32. https://doi.org/10.1016/S0140-6736(10)60835-5.
24. Roberts I, Shakur-Still H, Aeron-Thomas A, Belli A, Brenner A, Chaudary MA, Chaudhri R, Jamaluddin SFB, Frimley L, Javaid K, Jooma R, Kayani A, Leech C, Mahmood K, Mansukhani R, Noor JM, Mejia-Mantilla J, Moss P, Pott J, et al. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019;394(10210):1713–23. https://doi.org/10.1016/S0140-6736(19)32233-0.
25. Rowell SE, Meier EN, McKnight B, Kannas D, May S, Sheehan K, Bulger EM, Idris AH, Christenson J, Morrison LJ, Frascone RJ, Bosarge PL, Colella MR, Johannigman J, Cotton BA, Callum J, McMullan J, Dries DJ, Tibbs B, et al. Effect of out-of-hospital tranexamic acid vs placebo on 6-month functional neurologic outcomes in patients with moderate or severe traumatic brain injury. JAMA. 2020;324(10):961–74. https://doi.org/10.1001/jama.2020.8958.
26. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med. 2009;37(Suppl 7):S186. https://doi.org/10.1097/CCM.0b013e3181aa5241.
27. Andrews PJD, Sinclair HL, Rodriguez A, Harris BA, Battison CG, Rhodes JKJ, Murray GD. Hypothermia for intracranial hypertension after traumatic brain injury. N Engl J Med. 2015;373(25):2403–12. https://doi.org/10.1056/NEJMoa1507581.
28. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care, AANS/CNS,

Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW. Guidelines for the management of severe traumatic brain injury. II. Hyperosmolar therapy. J Neurotrauma. 2007;24(Suppl):1. https://doi.org/10.1089/neu.2007.9994.

29. Olah E, Poto L, Hegyi P, Szabo I, Hartmann P, Solymar M, Petervari E, Balasko M, Habon T, Rumbus Z, Tenk J, Rostas I, Weinberg J, Romanovsky AA, Garami A. Therapeutic whole-body hypothermia reduces death in severe traumatic brain injury if the cooling index is sufficiently high: meta-analyses of the effect of single cooling parameters and their integrated measure. J Neurotrauma. 2018;35(20):2407–17. https://doi.org/10.1089/neu.2018.5649.
30. James Cooper D, Nichol AD, Bailey M, Bernard S, Cameron PA, Pili-Floury S, Forbes A, Gantner D, Higgins AM, Huet O, Kasza J, Murray L, Newby L, Presneill JJ, Rashford S, Rosenfeld JV, Stephenson M, Vallance S, Varma D, Webb SAR, Trapani T, Mcarthur C, POLAR Trial Investigators and the ANZICS Clinical Trials Group. Effect of early sustained prophylactic hypothermia on neurologic outcomes among patients with severe traumatic brain injury the polar randomized clinical trial. JAMA. 2018;320(21):2211–20. https://doi.org/10.1001/jama.2018.17075.
31. 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. J Trauma Acute Care Surg. 2017;83(3):496–506. https://doi.org/10.1097/TA.0000000000001571.
32. Yndrome S, Etwork N. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301–8. https://doi.org/10.1056/nejm200005043421801.
33. Huber-Lang M, Lambris JD, Ward PA. Innate immune responses to trauma review-article. Nat Immunol. 2018;19(4):327–41. https://doi.org/10.1038/s41590-018-0064-8.
34. Petrucci N, De Feo C. Lung protective ventilation strategy for the acute respiratory distress syndrome. Cochrane Database Syst Rev. 2013;(2):CD003844. https://doi.org/10.1002/14651858.CD003844.pub4.
35. Offner PJ, Moore EE, Ciesla D, Hoyt D, Moore F, Peterson S. The adrenal response after severe trauma. Am J Surg. 2002;184(6):649–53. https://doi.org/10.1016/S0002-9610(02)01101-7.
36. Hoover L, Bochicchio GV, Napolitano LM, Joshi M, Bochicchio K, Meyer W, Scalea TM. Systemic inflammatory response syndrome and nosocomial infection in trauma. J Trauma Injury Infect Crit Care. 2006;61(2):310–6. https://doi.org/10.1097/01.ta.0000229052.75460.c2.
37. Lepelletier D, Roquilly A, Demeure Dit Latte D, Mahe PJ, Loutrel O, Champin P, Corvec S, Naux E, Pinaud M, Lejus C, Asehnoune K. Retrospective analysis of the risk factors and pathogens associated with early-onset ventilator-associated pneumonia in surgical-ICU head-trauma patients. J Neurosurg Anesthesiol. 2010;22(1):32–7. https://doi.org/10.1097/ANA.0b013e3181bdf52f.
38. Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troché G, Chaumet-Riffaut P, Bellissant E. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. J Am Med Assoc. 2002;288(7):862–71. https://doi.org/10.1001/jama.288.7.862.
39. Keh D, Boehnke T, Weber-Cartens S, Schulz C, Ahlers O, Bercker S, Volk HD, Doecke WD, Falke KJ, Gerlach H. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. Am J Respir Crit Care Med. 2003;167(4):512–20. https://doi.org/10.1164/rccm.200205-446OC.
40. Roquilly A, Mahe PJ, Seguin P, Guitton C, Floch H, Tellier AC, Merson L, Renard B, Malledant Y, Flet L, Sebille V, Volteau C, Masson D, Nguyen JM, Lejus C, Asehnoune K. Hydrocortisone therapy for patients with multiple trauma: the randomized controlled HYPOLYTE study. JAMA. 2011;305(12):1201–9. https://doi.org/10.1001/jama.2011.360.
41. Wahl WL, Taddonio M, Maggio PM, Arbabi S, Hemmila MR. Mean glucose values predict trauma patient mortality. J Trauma Injury Infect Crit Care. 2008;65(1):42–7. https://doi.org/10.1097/TA.0b013e318176c54e.

42. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359–67. https://doi.org/10.1056/NEJMoa011300.
43. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–97. https://doi.org/10.1056/NEJMoa0810625.
44. Marik PE, Preiser JC. Toward understanding tight glycemic control in the ICU: a systematic review and metaanalysis. Chest. 2010;137(3):544–51. https://doi.org/10.1378/chest.09-1737.
45. Hermanides J, Plummer MP, Finnis M, Deane AM, Coles JP, Menon DK. Glycaemic control targets after traumatic brain injury: a systematic review and meta-analysis. Crit Care. 2018;22(1):11. https://doi.org/10.1186/s13054-017-1883-y.
46. Macrae D, Grieve R, Allen E, Sadique Z, Morris K, Pappachan J, Parslow R, Tasker RC, Elbourne D. A randomized trial of hyperglycemic control in pediatric intensive care. N Engl J Med. 2014;370(2):107–18. https://doi.org/10.1056/nejmoa1302564.
47. Marik PE, Varon J. Intensive insulin therapy in the ICU: is it now time to jump off the bandwagon? Resuscitation. 2007;74(1):191–3. https://doi.org/10.1016/j.resuscitation.2007.01.023.
48. Kudsk KA. Beneficial effect of enteral feeding. Gastrointest Endosc Clin N Am. 2007;17(4):647–62. https://doi.org/10.1016/j.giec.2007.07.003.
49. Reignier J, Boisramé-Helms J, Brisard L, Lascarrou JB, Ait Hssain A, Anguel N, Argaud L, Asehnoune K, Asfar P, Bellec F, Botoc V, Bretagnol A, Bui HN, Canet E, Da Silva D, Darmon M, Das V, Devaquet J, Djibre M, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet. 2018;391(10116):133–43. https://doi.org/10.1016/S0140-6736(17)32146-3.
50. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, Van Cromphaut S, Ingels C, Meersseman P, Muller J, Vlasselaers D, Debaveye Y, Desmet L, Dubois J, Van Assche A, Vanderheyden S, Wilmer A, Van den Berghe G. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011;365(6):506–17. https://doi.org/10.1056/nejmoa1102662.
51. Doig GS, Simpson F, Sweetman EA, Finfer SR, Cooper J, Heighes PT, Davies AR, O'Leary M, Solano T, Peake S. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA. 2013;309(20):2130–8. https://doi.org/10.1001/jama.2013.5124.
52. Marik PE, Zaloga GP. Immunonutrition in critically ill patients: a systematic review and analysis of the literature. Intensive Care Med. 2008;34(11):1980–90. https://doi.org/10.1007/s00134-008-1213-6.
53. Van Zanten ARH, Sztark F, Kaisers UX, Zielmann S, Felbinger TW, Sablotzki AR, De Waele JJ, Timsit JF, Honing MLH, Keh D, Vincent JL, Zazzo JF, Fijn HBM, Petit L, Preiser JC, Van Horssen PJ, Hofman Z. High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomized clinical trial. JAMA. 2014;312(5):514–24. https://doi.org/10.1001/jama.2014.7698.
54. Gu WJ, Deng T, Gong YZ, Jing R, Liu JC. The effects of probiotics in early enteral nutrition on the outcomes of trauma: a meta-analysis of randomized controlled trials. J Parenter Enter Nutr. 2013;37(3):310–7. https://doi.org/10.1177/0148607112463245.
55. Barraud D, Bollaert PE, Gibot S. Impact of the administration of probiotics on mortality in critically ill adult patients: a meta-analysis of randomized controlled trials. Chest. 2013;143(3):646–55. https://doi.org/10.1378/chest.12-1745.

Future Directions

20

Roberta Iadarola and Fausto Catena

20.1 Background

Although the leading immediate causes of death following severe trauma are brain injury and hemorrhage, many trauma victims later die following complications such as MOF or sepsis, with the individual's immune response to injury significantly influencing the chances of developing these life-threatening conditions [1].

Two opposing clinical syndromes characterize the immune and inflammatory response to traumatic injury: systemic inflammatory response syndrome (SIRS) and compensatory anti-inflammatory response syndrome (CARS). The immune response that develops during the SIRS and CARS responses is complex and involves the innate and adaptive arms of the immune system. Moore and colleagues proposed that MOF was a bimodal phenomenon [2]. In the 1-event model, a massive traumatic insult induces SIRS characterized by elevated levels of circulating proinflammatory cytokines and immune cell activation with associated precipitates organ dysfunction (OD). By other side in the same time trauma could induce CARS, characterized by raised anti-inflammatory cytokines and immune paresis develops.

Patients initially resuscitated into moderate SIRS become vulnerable to a second activating event (infections, embolism, transfusions, secondary operations, etc.) during CARS and could develop late MOF [3]. As classic full-blown MOF is getting less frequent, a new OD phenotype emerged among patients discharged after lengthy intensive care unit (ICU) stays to long-term facilities, where they developed

R. Iadarola (✉)
Abdominal Surgery Department, IRRCS Casa sollievo della sofferenza Hospital, San Giovanni Rotondo, FG, Italy

Department of Surgery and Emergency, Maggiore, The institution is Bufalini Hospital Cesena, Parma, Italy

F. Catena
Department of Surgery and Emergency, Maggiore, The institution is Bufalini Hospital Cesena, Parma, Italy

Z. J. Balogh et al. (eds.), *Postinjury Multiple Organ Failure*, Hot Topics in Acute Care Surgery and Trauma, https://doi.org/10.1007/978-3-030-92241-2_20

a persistent inflammation immunosuppression catabolism syndrome (PICS) [4] not to be confused with the post-intensive care syndrome.

The incidence of PICS was 4.7 per 1000 multitrauma patients. PICS is characterized by chronic low-grade inflammation, suppressed host immunity, and a loss of lean body mass, despite nutritional intervention [5].

Clinically, PICS is defined as long ICU stay (>14 days), persistent inflammation (C-reactive protein concentration >150 mg/dL and retinol binding protein concentrations <10 mg/dL), immunosuppression (total lymphocyte count <800/mm), and a catabolic state (serum albumin level <3.0 mg/dL, creatinine height index <80%, and weight loss >10% or body mass index <18 kg/m during the current hospitalization). Laboratory tests show persistent neutrophilia and lymphopenia. Discharged to long-term care facilities, patients with PICS die an indolent death or experience sepsis recidivism and ICU readmission (see Fig. 20.1). Clinical risk factors described so far include a poor premorbid health status and an age of 65 years and above. This data is particularly important because the elderly population is growing in ICU. Elderly patients with baseline comorbidities and sarcopenia are especially prone to this refractory clinical phenotype. Often, the long-term outcome involves impairment of cognitive and functional status from which recovery is uncertain. Studies are underway to better define the phenotype, its true significance, and novel interventions to prevent it or its progression. As the population ages, PICS is likely to be the next challenge in surgical critical care [5].

20.2 How Major Injury Influences the Immune System?

The immune response that develops during the SIRS and CARS responses is complex and involves the innate and adaptive arms of the immune system, with significant alterations apparent in the composition, phenotype, and/or function of the circulating immune cell pools. For example, following major injury, marked alterations have been described in the antimicrobial functions of neutrophils, the surface

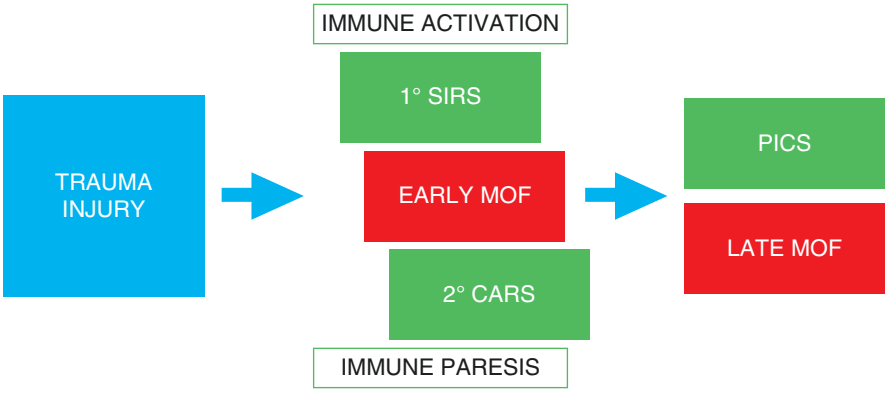


Fig. 20.1 Succession of SIRS, CARS, and PICS after traumatic injury

phenotype of monocytes, and the absolute number of circulating lymphocytes [1]. The current paradigm for how major injury influences the immune system is based almost entirely upon the analysis of blood samples obtained from patients post-hospital admission and several hours postinjury. How trauma-induced changes in immunity during the ultra-early postinjury phase (particularly within the first hour) are limited.

20.2.1 Ultra-Early Immune Trauma Changes

Understand the immune status of trauma patients prior to their arrival at hospital would provide the evidence base for early intervention to improve patient outcomes or stratification for treatment. The patients who experience poor clinical outcomes following traumatic injury elicit a more robust and prolonged immune/inflammatory response than those who report better outcomes.

Analysis of whole blood cell counts revealed a significant leukocytosis within minutes of traumatic injury with neutrophilia. After 48–72-h postinjury time points, the lymphocyte counts were significantly lower than the values for healthy controls (HCs) and we found a significantly increased frequency and absolute number of CD16 CD62L neutrophils (immunosuppressive properties) relative to the values recorded for HCs. Traumatic injury is associated with immediate alterations in lipopolysaccarides LPS-induced cytokine production by whole blood leukocytes that persist into the acute postinjury phase. In confront to HCs, significantly lower concentrations are recorded for IL-6, TNF-α, and MCP-1. Compared to the values recorded for HCs, trauma patients presented in the immediate aftermath injury with a significantly higher absolute number of CD14 + HLA-DR-monocytes, a subset that has been shown to have immune suppressive properties These data, are associated with and/or predictive of mortality, multiple organ dysfunction/failure, and sepsis, suggest a potential role for immune monitoring in identifying patients at risk of poor outcome [1].

20.2.2 Gut Microbiota and Trauma: Concept of Pathobiome

Through novel methods of characterizing microbial community composition, an enhanced understanding of the relationship between commensal organisms and human health is emerging across medical specialties and scientific disciplines. This understanding has led to promising diagnostic and even therapeutic modalities; perhaps the most widely recognized application is that of fecal transplant in colitis due to *Clostridium difficile*. This could be very interesting in trauma populations. Despite resuscitation, in trauma patients, gut dysfunction promotes distant organ injury. In addition, post-resuscitation nosocomial and iatrogenic “hits” exaggerate the immune response, contributing to MOF. This was a provocative concept, suggesting infectious and noninfectious causes of inflammation may trigger, heighten, and perpetuate an inflammatory response culminating in MOF and death. Emerging

evidence suggests post-traumatic injury mechanisms, such as intestinal mucosal disruption and shifting of the gut microbiome to a pathobiome [6]. In health, the major function of the epithelial lining of the gastrointestinal tract is to act as a filter, allowing absorption of required nutrients, but barring bacteria, macromolecules, and toxic compounds. Gut dysfunction in the trauma patient has long been recognized as a constellation of alterations in intestinal transit and luminal nutrient transporters, mucosal ischemia, and disuse-associated villus atrophy, resulting in overall reduction in mucosal surface area with loss of barrier function and increased permeability [6]. Disturbances in this barrier may lead to enhanced uptake of a host of toxic substances, including inflammatory molecules, pathogenic bacteria, and antigens, from the intestinal lumen into the bloodstream, thereby promoting a state of chronic low-level inflammation [7]. As intestinal permeability increases and proinflammatory cytokines, such as TNF-α, IL-1, and IL-6, are released into the systemic circulation, fluid is extravasated from the gut, and extravascular edema occurs. Moreover, proinflammatory cytokines induce changes in tight junction proteins in the gut, leading to hyperpermeability. In healthy individuals, the intestine contains a large microbiome populated with commensal bacteria. In addition to the loss of the intestinal barrier function, during sepsis and MODS, this population shifts to include more virulent and pathogenic bacteria, altering the complex crosstalk between the immune system, microbiome, and intestinal epithelium resulting in dysbiosis and a dysregulated immune response. Indeed early culture of gut flora in intensive care unit (ICU) patients would suggest that microbial composition at the time of admission may correlate to critical outcomes. Howard et al. hypothesized that in critically injured patients, the gut microbiome would undergo significant compositional changes in the first 72 h after injury. Members of the bacterial orders Bacteroidales, Fusobacteriales, and Verrucomicrobiales were depleted during 72 h, whereas Clostridiales and Enterococcus members enriched significantly. The findings of rapid microbiome changes after severe injury indicate that commensal microbial populations undergo significant changes early in the course of resuscitation and stabilization after trauma [8]. The correlation of microbiota composition to clinical features, course, and outcomes represents an area of active ongoing research and may represent an area in which the care of the injured patient might be optimized. Implementing a probiotic regimen or guiding the microbial composition changes after trauma might prove a powerful tool in the critical care arsenal. Effectively, the gastrointestinal tract serves to hasten MOF, and altered levels of citrulline and intestinal fatty acid–binding proteins are markedly elevated in critically ill patients. All of this culminates in enhanced apoptosis, particularly in intestinal and pulmonary epithelial cells. Armacki et al. support a role for TNK1 (porcine murine models) in the progression from intestinal apoptosis and gut failure to bacterial translocation, sepsis, and MODS and adds another possible mechanism for progression. Despite these preliminary findings, caution needs to be taken in extrapolating these results to humans. Future clinical studies that target TNK1 in the intensive care unit (ICU) setting of sepsis and subsequent monitoring are required to determine if this approach is able to prevent multiple organ damage in critically ill patients [9].

20.2.3 Gut Microbiomes and Lungs (Gut–Lung axis)

Mucosal lining of respiratory and gastrointestinal tract is de facto continuous, allowing micro-aspiration of oropharyngeal flora to normally occur even in healthy individuals. The anaerobes which in this way enter alveolar spaces are typically non-pathogenic constituents of normal oral flora. In critically ill patients, gut microbiome undergoes substantial changes and might increasingly translocate across the bowel wall and even enter the lung [10, 11]. The phenomenon of "more of the gut in the lung" appears clinically important, as this microbiome shift is associated with increased markers of adverse inflammation and lung injury. Recent evidence suggests that an altered lung microbiome might promote inflammation and lung parenchymal injury in ARDS [12]. How do the gut microbes enter the lungs of critically ill? Translocation, rather than aspiration, was the primary mechanism of microbial gut entry to the lung. While definitive data are yet lacking, it has been proposed that the route of bacterial migration might involve gut-draining lymphatics, portal, or systemic circulation. The ideal interventions in sepsis and ARDS would not only target the adverse inflammation but also simultaneously restore the immune competence as well as normal composition of altered microbiomes. Conversely, the microbes causing infection or the ones promoting adverse inflammation would be targeted by a highly specific antibiotic therapy. Small steps have already been taken in some of these directions. Clinical trials with immune checkpoint inhibitors (PD-1 antagonist), drugs that are now broadly used in cancer immunotherapy are currently ongoing in sepsis [13]. Reversing the "immune exhaustion" by these drugs in the right patient populations might be beneficial in reducing opportunistic infections and recurrent sepsis episodes [12].

20.2.4 Brain Trauma and Gut (Brain–Gut Axis)

The brain–gut axis (BGA) is a communication network that links together the central nervous system (CNS) and the enteric nervous system (ENS) [14]. Physiological effects following trauma brain injury (TBI) have been increasingly studied, with intestinal dysfunction representing an important consequence [15, 16]. The disruption of the brain–gut axis, the major bidirectional communication pathway between the brain and the gastrointestinal system, which incorporates both afferent and efferent signals involving neuronal, hormonal, and immunologic pathways, can result in sequelae such as chronic dysfunction of the gastrointestinal system and disability [17]. The changes in the gut microbiota would potentiate autoimmune processes or, alternatively, protect against proinflammatory conditions in the central nervous system. Evidence from multiple pre-clinical studies suggests that commensal gut microbiota affect the intestinal immune response. Commensals influence gut-associated lymphatic tissue (GALT) formation, induction of Peyer's patches with induction of mucosal T cells and IgA plasma cells. Investigation into the BGA in the setting of systemic injury and TBI has identified several promising targets for intervention. One possible treatment involves mitigating the gut dysbiosis that results

from TBI by attempting to restore the normal gut microbiota. Fecal microbiota transplant (FMT) is one method of addressing this problem and involves taking fecal matter from a donor, mixing it with a solution, and placing the strained fecal solution into a patient to replace the lost beneficial bacteria. Not thoroughly explored for TBI, probiotics may offer another potential therapeutic option by increasing IL-10 production and decreasing intestinal epithelial cell production of proinflammatory cytokines [18]. In addition, probiotics have also been found to reduce intestinal permeability through modulating the hypothalamic–pituitary–adrenal (HPA) axis. Brenner et al.'s systematic review also found positive results correlated with probiotic and prebiotic interventions, noting effects such as increased regulatory T cells, improved immunoregulation, and decreased stress and inflammation. Finally, use of particular enteral antibiotics following TBI can counter dysbiosis and induce neuroprotection by increasing T reg cell populations [19, 20]. Nutritional interventions are also being explored. In addition, in 2011, the Institute of Medicine recommended that patients with TBI should be given a high level of *nutrition in terms of calories and quality*, for 2 weeks to curtail inflammation. Dietary treatments in the form of early enteral nutrition and intake of glutamine, arginine, nucleotides, and omega-3 fatty acids are another potential therapy that stimulates immune cells and promotes gut barrier health. Vitamins and minerals such as nicotinamide, zinc, and magnesium have also shown potential in pre-clinical models.

20.2.5 Spinal Cord Trauma and Gut

Spinal cord injury (SCI) causes gut dysbiosis and that dysbiosis impairs functional recovery and exacerbates intraspinal inflammation and lesion pathology. The continuing analyses of genomic and metagenomic changes in gut microbiota will allow scientists to map the dynamic patterns of dysbiosis caused by SCI. Data from these analyses can then be used to estimate how the biological functions attributed to specific gut microbiota (e.g., metabolism of amino acids by Lactobacilli) are affected by SCI and whether these and other changes can predict the probability or severity of various SCI comorbidities including infection, anemia, obesity/metabolic syndrome, and, perhaps, secondary neurological deterioration or improvement. Restoring effective dialogue between the spinal cord, gut, and immune system would undoubtedly improve recovery and/or quality of life for individuals living with SCI. However, repair of the injured spinal cord is a formidable therapeutic target. Both the gut and immune system are more tractable targets and since each is affected by changes in the gut microbiota, efforts to modify postinjury gut dysbiosis could have therapeutic value. In this context, oral probiotics must be considered for use in human SCI. Recently, using a mouse model of SCI, we showed that sustained postinjury delivery a medical-grade probiotic (composed by Lactobacillus and Bifidobacterium) improved immune function and promoted recovery of locomotor function [21]. These and other probiotic bacteria exert diverse effects throughout the body. In addition to their immunomodulatory effects, Lactobacillus and Bifidobacterium produce neuroactive metabolites (butyrate and other short-chain

fatty acids) and neurotransmitters (serotonin, dopamine, γ-aminobutyric acid), These neurometabolites, produced locally in the gut, can spill over into the circulation where they can influence systemic inflammation and immune function. These also can bypass the blood–brain barrier to affect CNS structure and function. Data from our laboratory show that SCI mice fed probiotics daily for 5 weeks show improvements in spontaneous locomotor recovery with reduced neuropathology. Importantly, in the mesenteric lymph nodes of VSL#3-treated mice, CD4+CD25+FoxP3+ regulatory T cells (Tregs) increased significantly. Tregs, a population of T lymphocytes that express the transcription factor FoxP3, play a crucial role in immune homeostasis; Tregs actively suppress potentially damaging self-reactive (autoreactive) T cells. The continuing analyses of genomic and metagenomic changes in gut microbiota will allow scientists to map the dynamic patterns of dysbiosis caused by SCI [22].

20.2.6 Strategies to Reverse Gut Dysfunction and Its Consequences

20.2.6.1 Immunonutrition

Enteral Nutrition

Enteral nutrition, as opposed to parenteral nutrition, has been shown to improve gut barrier function and immunity and reduce bacterial virulence. In animal models of trauma, burn, and sepsis-induced shock, provision of enteral nutrition demonstrated improved splanchnic blood flow, improved intestinal mucosal microcirculation, improved hepatic blood flow, improved hepatic and splanchnic oxygenation, improved bioenergetics, reduced bacterial translocation, and improved survival. Early randomized controlled trials (RCTs) of enteral nutrition versus parenteral nutrition in trauma patients demonstrated significant reductions in infectious complications with enteral nutrition [6]. Evidence supports that early enteral nutrition (EEN) is not only feasible but also associated with decreased incidence of nosocomial infection because it induces a complex immunologic response. EEN supports the function of the mucosal-associated lymphoid tissue (MALT), which produces 70% of the body's secretory immunoglobulin A (IgA) [23]. Naive T and B cells target and enter the gut-associated lymphoid tissue (GALT) where they are sensitized and stimulated by antigens sampled from the gut lumen and thereby become more responsive to potential pathogens in the external environment. These stimulated T and B cells then migrate via mesenteric lymph nodes and the thoracic duct and into the vascular tree for distribution to GALT and extraintestinal sites of MALT. Lack of enteral stimulation (i.e., use of total parenteral nutrition [TPN]) causes a rapid and progressive decrease in T and B cells within GALT and simultaneous decreases in intestinal and respiratory IgA levels. Previously resistant TPN-fed laboratory animals, when challenged with pathogens via respiratory tree inoculation, succumb to overwhelming infections. These immunologic defects and susceptibility to infection are reversed within 3–5 days after initiating EN. Feeding

the gut in critically ill patients has been shown to reverse shock-induced mucosal hypoperfusion and impaired intestinal transit as well as attenuate gut permeability defects and lessen the severity of CARS.

Lipid-Rich Enteral Nutrition

Lipid-rich enteral nutrition has been demonstrated to minimize gut injury by activating cholecystokinin-1 (CCK-1) receptor activity in the gut, through stimulation of the cholinergic anti-inflammatory pathway [24, 25]. Ingestion of a high-lipid formulation stimulates CCK-1 receptor and activates a central nervous system reflex arch via the vagus nerve to release acetylcholine. The acetylcholine binds to nicotinic receptors on macrophages to reduce proinflammatory cytokine production and suppress cytokine-mediated inflammation, as seen in septic and hemorrhagic shock.

Immunonutrition: Glutamine

Immunonutrition refers to macronutrients and micronutrients that can alter or attenuate the immune and/or inflammatory response and has been associated with reduced infectious complications in critically ill patients. Although arginine, omega-3 fatty acids, and nucleotides have been studied in the critical care setting, glutamine has probably been the best studied for use in gut dysfunction. In health, glutamine is the most abundant free amino acid. During critical illness, skeletal muscle releases glutamine into circulation, and levels are depleted, rendering it a conditionally essential amino acid. Glutamine is a preferred source of fuel for enterocytes and GALT [26].

Protease Inhibitors

Pancreatic serine proteases have been associated with intestinal mucus layer disruption and are biologically active factors contained in mesenteric lymph nodes that modulate downstream organ dysfunction, such as acute lung injury. Serine protease inhibitors, such as nafamostat and tranexamic acid (TXA), have been used to preserve the intestinal mucus layer [27]. TXA is an antifibrinolytic agent (and serine protease inhibitor) that has been used in numerous surgical populations to reduce bleeding. It was demonstrated that addition of systemic TXA after a hypoxic event protected the intestinal mucus layer. In a rat model of hemorrhagic shock, intraluminal TXA significantly reduced gut and lung histopathologic injury and inflammation in rats given TXA, when compared with hemorrhagic shock alone [27]. Clinical studies will need to confirm this before wide usage can be justified.

20.2.6.2 Fecal Microbiota Transplant (FMT)

Fecal microbiota transplantation (FMT), defined as the transfer of a microbial community from a healthy donor to a patient, has emerged as a promising treatment option for a range of chronic disorders [28, 29], especially of the Clostridium difficile infection. Kassam with colleagues [30] performed a meta-analysis and systematic review to investigate the efficacy and safety profile of fecal microbiota transplantation in Clostridium difficile infection. They included 11 studies with 273 patients in their review and came to the conclusion that FMT were useful for the

treatment of Clostridium difficile infection with no reported adverse events associated with this therapy. The success of treatment of recurrent Clostridium difficile infection with donor feces made fecal microbiota transplantation emerge as a promising effective treatment option for a range of chronic disorders. Though FMT appears to be safe, yet few short-term adverse effects and complications attributed to the procedure were reported. Although FMT has high success rates with long-term durability, few disadvantages still exist. In particular, the manipulation of feces and the classical enteral administration methods are not only laborious but tend to make the procedure rather unattractive for physicians and patients. In the context of these disadvantages, few efforts have been made to enhance the feasibility and social acceptance of microbiota transplantation. FMT may be administered via enemas or as a slurry given via a nasogastric tube [31]. Not yet tested, this could be very interesting in trauma populations.

20.2.6.3 Probiotic

"Probiotics" is a very general term used to describe many different species and strains of healthy microbes. They are living organisms that, when taken internally, can produce an immunomodulating effect and improve the gastrointestinal (GI) mucosal barrier. *Lactobacillus* and *Bifidobacterium* are the most commonly found organisms. Although many health care clinicians believe that probiotics have certain benefits for their patients, many are reluctant to use them for patients or in clinical trials. The FDA does not provide strict oversight over the use of probiotics, as they usually are considered a supplement. Much of the research on probiotic use has been conducted on otherwise healthy individuals. With the growing interest in probiotic supplementation for the benefit of strengthening and altering host immunity, recent research has been conducted in the inpatient setting on acutely ill patients with the goal of preventing infections. The majority of hospital research that has been conducted with probiotics is with their use for the prevention of antibiotic-associated diarrhea and *Clostridium difficile* (*C. diff*) infections. Another area of inpatient probiotics research is for the prevention of ventilator-associated pneumonia (VAP). Research with trauma patients is fairly new, so there are very few published studies. Outcome assessment for these studies not only generally focused on overall hospital-acquired infections but also examined secondary outcomes such as VAP, length of stay (both intensive care unit [ICU] and hospital), and mortality rates. Results of these randomized controlled trials showed that the administration of probiotics to trauma patients has positive outcomes for these patients [32–35].

20.2.7 Potential Risks Associated with Probiotics Use

Because probiotics have been primarily used by healthy people to improve GI function, their use in acutely ill patients does not come without controversy. The most commonly reported adverse effect associated with their consumption is mild GI effects such as abdominal cramps, flatulence, and nausea. Because probiotics are living organisms, typically composed of bacteria and fungi, they theoretically could

stimulate an excessive immune response in certain susceptible individuals or could cause an infectious process if they somehow establish outside of the GI system [33].

20.3 Adrenal Insufficiency and Cortisol Replacement Therapy

Adrenal insufficiency (AI) occurs frequently in trauma and is associated with increased mortality but often is underrecognized and the impact poorly understood. Critical illness-related corticosteroid insufficiency (CIRCI) is a concept that was first introduced in 2008 by an international multidisciplinary task force convened by the Society of Critical Care Medicine (SCCM) to describe impairment of the hypothalamic pituitary axis (stress response) during critical illness. CIRCI is characterized by dysregulated systemic inflammation resulting from inadequate intracellular glucocorticoid-mediated anti-inflammatory activity for the severity of the patient's critical illness. International guidelines recommend that AI should be suspected in hypotensive patients responding poorly to fluids and vasopressor agents, with laboratory signs of compromised adrenal function [3].

The symptoms of CIRCI are listed in Table 20.1. CIRCI is associated with increased circulating levels of biological markers of inflammation and coagulation over time, morbidity, length of ICU stay, and mortality. This guideline by 16 experts task force in 2008 focuses on the three disorders that most clinicians associate with CIRCI: sepsis/septic shock, acute respiratory distress syndrome, and major trauma [36]. The 2008 guidelines suggested that the diagnosis of CIRCI is best made by a delta total serum cortisol of <9 μg/dL after IV cosyntropin (250 μg) administration or a random total cortisol of <10 μg/dL [37].

Table 20.1 The clinical symptoms of CIRCI

Neurological	Confusion
	Delirium
	Coma
Cardiovascular	Hypotension refractory to fluid resuscitation
	Decreased sensitivity to catecholamines
	High cardiac index
Digestive	Nausea
	Vomiting
	Intolerance to enteral nutrition
Respiratory	Persistent hypoxia
Laboratory	Hypoglycemia
	Hyponatremia
	Hyperkalemia
	Metabolic acidosis
	Hypereosinophilia
Imaging	Hemorrhage or necrosis in hypothalamus, pituitary gland, or adrenal gland

20.3.1 CIRCI in Septic Shock

The task forces suggests using corticosteroids in patients with septic shock that is not responsive to fluid and moderate to high-dose vasopressor therapy. Given the consistent effect of corticosteroids on shock reversal and the low risk for superinfection with low-dose corticosteroids, the task force suggests the use of low-dose IV hydrocortisone <400 mg/day for at least 3 days at full dose, or longer in adult patients with septic shock that is not responsive to fluid and moderate to high-dose (>0.1 μg/kg/min of norepinephrine or equivalent) vasopressor therapy (conditional recommendation, low quality of evidence).

20.3.2 CIRCI in ARDS

Acute respiratory distress syndrome (ARDS) represents an important public health problem globally. Despite advances in supportive care, ARDS is associated with a high mortality rate (35–45%) [38]. ARDS is also associated with high costs of inpatient care and significant long-term morbidity and resource utilization. The task forces suggests use of corticosteroids in patients with early moderate to severe acute respiratory distress syndrome (PaO/FiO of <200 and within 14 days of onset) (conditional recommendation, moderate quality of evidence).

20.3.3 CIRCI in Major Trauma

Major trauma is the main cause of non-septic systemic inflammatory response syndrome (SIRS). Tissue necrosis, hemorrhage, and ischemia–reperfusion injury are the main factors that trigger the inflammatory cascade. CIRCI may be common in severe trauma patients and is associated with uncontrolled inflammation, vasopressor dependency, and poor clinical outcomes. The study included 19 trials that investigated the effects of corticosteroids on short-term mortality in adults with multiple trauma. There were 1691/6286 (26.9%) deaths in the corticosteroid group versus 1401/5983 (23.4%) deaths in the placebo group (RR = 1.00, 95% CI 0.89–1.13). The task force members suggest against the use of corticosteroids in major trauma because they have no effect on mortality in trauma patients (conditional recommendation, low quality of evidence).

20.4 Insulin and Glycemic Control

Hyperglycemia and insulin resistance are common in critically ill patients, even when glucose homeostasis has previously been normal. Increased gluconeogenesis, despite abundantly released insulin, is probably central to this disruption of gluco

regulation. Hence, the liver seems to be a major site of insulin resistance. Reduced insulin-stimulated glucose uptake also exists in skeletal muscle and heart. Overall glucose uptake, however, is increased but takes place mainly in insulin-independent tissues such as the brain, the red blood cells, and in wounds. Even moderate hyperglycemia, between 110 and 200 mg/dL, in diabetic and in non-diabetic critically ill patients is directly or indirectly harmful to vital organs and systems, thus contributing to adverse outcome. Strict maintenance of normoglycemia with intensive insulin therapy has been shown to reduce intensive care and hospital mortality and morbidity of critically ill adult patients in a surgical ICU [39].

The management of hyperglycemia in critically ill patients has been extensively studied in a number of clinical settings. Findings to date, however, have failed to demonstrate consistent data for improved patient outcomes with a variety of glycemic management strategies [40, 41].

Van den Berghe et al. [42] were among the early advocates for intensive insulin control, demonstrating that targeting a serum blood glucose of <110 mg/dL decreased morbidity and mortality in a surgical critical care population. Follow-up studies, most notably the NICE-SUGAR study (Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation), which compared intensive glucose management with conventional management, failed to replicate the findings of Van den Berghe et al. and, in fact, showed evidence of increased harm, largely secondary to a high incidence of severe hypoglycemia [43].

20.4.1 Lactate and Trauma

While less controversial than glucose management, management of lactate elevation has been extensively studied in the trauma literature. As Richards et al. [44] describe, serum lactate levels may become elevated secondary to the physiologic stress response via a separate metabolic pathway, independent of the effects of shock and organ hypoperfusion. An elevated serum lactate, in particular an inability to achieve adequate lactate clearance, has been associated with poor clinical outcomes in the trauma population [45]. A variety of resuscitation strategies, including careful vasopressor administration to ensure adequate end-organ perfusion, balanced fluid and blood product administration, and avoiding excessive volume resuscitation, have all been extensively studied and correlated to lactate clearance, with a demonstrable impact on clinical outcomes. Other studies are urgently needed to better understand how glucose and resuscitation strategies impact the correlation among hyperglycemia, elevated lactate, and MOF [46].

20.5 Toll-Like Receptors (TLRs)-Directed Interventions

The 1994 “danger theory” of the inflammatory response following trauma or infection proposed that the immunological system’s role was to protect the body from danger. In this model, immunological responses are triggered by specific types of

cell death. If a healthy, undamaged cell dies an apoptotic death, it is scavenged without triggering an immune response. Conversely, cell lysis or apoptosis via trauma or infection releases intracellular contents and signals "danger," triggering both innate and adaptive responses. The injured cell releases endogenous damage-associated molecular patterns (DAMPs), analogous to the microbial pathogen-associated molecular patterns (PAMPs), released in sepsis, both of which activate the innate immunity.

PAMPs are exogenous microbial molecules that alert the organism to pathogens and are recognized by cells of the innate and acquired immunity system, primarily through toll-like receptors (TLRs), and activate several signaling pathways [3].

Numerous reports have shown that both hemorrhagic shock and reperfusion injury (HS/R) and trauma activate immune system through pattern recognition receptors such as Toll-like receptors (TLR 4). This activation of the immune system is seen as a robust systemic inflammatory response, which can result in subsequent organ damage.

For this reason targeting TLRs may be a promising intervention strategy to reduce MOF. Yet, because TLR activation occurs through a variety of mechanisms, generating full antagonists is technically difficult.

The best-understood mechanism for TLR4 activation is by the pathogen-associated molecular pattern, lipopolysaccharide (LPS; endotoxin), which is found on the outer wall of gram-negative bacteria.

However, in the setting of sterile injury as seen in trauma, LPS is probably not the dominant activator of TLR4. Instead there is evidence that damage-associated molecular patterns (DAMP), such as high mobility group box 1 (HMGB1), released by damaged or stressed cells, drive TLR4 activation [47].

The development of Eritoran tetrasodium (E5564), a potent and full antagonist of LPS at TLR4, is a significant advance and offers hope that other TLR-selective antagonists may become available in future years.

Korff et al. investigate in animal models the effectiveness of Eritoran in reducing inflammation and organ dysfunction induced in two independent systemic models of injury: HS/R and bilateral femur fracture (BFF). They show here that Eritoran was able to prevent liver injury, as well as reduce gut barrier dysfunction in HS/R. Eritoran treatment also suppressed the early inflammatory response in both models. Thus Eritoran is an effective candidate for reducing organ damage not only in local ischemia models but also in models that lead to a robust systemic inflammatory response, such as trauma or hemorrhagic shock. This suggests that Eritoran may serve as a potential therapy in trauma and hemorrhagic shock and further confirms the importance of TLR4/MD2 signaling in hemorrhagic shock induced inflammation and organ injury [48].

20.6 Immunomodulation

For future development in therapeutic strategies for the prevention of sepsis and MODS, it is indispensable to understand the underlying pathophysiology mechanism. In the review article, Thompson et al. indicated immune dysfunction as a key risk factor for the late onset of infection, sepsis, and MODS after trauma [49]. In combat casualties, delaying suitable treatment may result in prolonged immune dysfunction with subsequent late complications, such as wound infection, delayed wound healing, sepsis, and MODS. With regard to the mechanism underlying immune depression, damage-associated molecular patterns (DAMPs) and large amounts of cytokines are initial factors that promote the disturbance of the immune response. Additionally, a lower expression of human histocompatibility leukocyte antigen (HLA)-DR on monocytes and lymphocyte dysfunction appears to be involved in the development of immune paralysis. Based on these theories, immunomodulation is revealed to be a better therapeutic strategy for septic complications in the setting of acute insults [38]. Emerging evidence from clinical trials has shown that some cytokines might be of potential benefit in regulating the host immune response, including granulocyte colony-stimulating factor (CSF)/granulocyte-macrophage CSF, interferon (IFN)-γ, interleukin (IL)-7, IL-15, thymosin α1, etc. Accumulated reports discover unidentified cytokines or reveal their novel roles in the immune response. The majority of the research is focused on the direct effects on immune cell differentiation or activation. Fan and his group [50] have recognized IL-25 as a crucial mediator in the inflammatory response in acute lung injury (ALI), which is a major component of MODS following trauma and infection.

Of note, mitochondrial function is critical for cell metabolism and energy production, and it appears to be associated with redox signaling, calcium flux, and apoptosis [51]. In trauma, hemorrhagic shock, and sepsis, hypoxia induces immune cell apoptosis and dysfunction, which greatly involves alterations in mitochondrial stability and function.

Accordingly, novel therapeutic strategies through the improvement of mitochondrial function are beneficial for protecting host immunity and organ function, such as mitochondrial membrane channel blockers, electric transport chain (ETC) enzymes, antioxidants, and biogenesis promotion reagents. The most attractive reagents among them are mitochondria-targeted coenzymes that have already been proven to be safe and are beneficial for various diseases.

20.6.1 Prehospital Immune Response

The current paradigm for how major injury influences the immune system is based almost entirely upon the analysis of blood samples obtained from patients' after admission and several hours postinjury. Indeed, with the exception of a small number of studies in which research samples were acquired at the scene of injury. Our knowledge of trauma-induced changes in immunity during the ultra-early postinjury phase (particularly within the first hour) is limited. Indeed, of the prehospital

based studies, only 1 investigated immune function, reporting a significant impairment in lipopolysaccharide (LPS)-induced cytokine production by whole blood leukocytes within minutes of injury, suggesting that trauma patients are immune suppressed even prior to hospital admission [52].

Although with small sample size (89 pt) the study by Hazeldine et al. has highlighted the dynamic nature of the immune response to trauma and shown at the functional and phenotypic level that immune alterations consistent with activation and suppression are evident within 1 h of injury, thus supporting the idea of an immediate and concomitant induction of the SIRS and CARS responses post-trauma [53].

20.7 The Glycocalyx and Trauma

The endothelial and epithelial glycocalyx (EG) has emerged as an important participant in both inflammation and immunomodulation. Shedding of the EG plays a central role in many critical illnesses. Degradation of the EG is associated with increased morbidity and mortality. We assume that trauma induced increases in plasma concentration of glycocalyx elements that are derived from shedding of the vascular endothelial surface. The endothelial glycocalyx plays an important role in vascular permeability by limiting protein and solvent flux into the cell junction; it regulates leukocyte and platelet interaction with adhesion cell molecules on the endothelial surface, thus influencing the local inflammatory cascade and the heparan sulfate component modulates the local cell surface coagulation system. Constituents of the glycocalyx have been used as biomarkers of injury severity and have the potential to be target(s) for therapeutic interventions aimed at immune modulation. The development of novel, glycocalyx-targeted polymers could represent a major advance for both protection of the glycocalyx from proteolytic degradation and restoration of the glycocalyx following shedding. Giantsos et al. [54] and Giantsos-Adams et al. [55] have demonstrated a proof-of-concept for developing glycocalyx-targeted polymers that enhance barrier properties, attenuate inflammation, and attenuate pressure-dependent mechanotransduction. The authors synthesized a 50–60 kDa water-soluble polymer (methacrylamidopropyl trimethylammonium chloride) that bound avidly to the endothelial surface and was devoid of any measurable in vitro toxicity. The polymer reduced endothelial hydraulic conductivity, reduced the pressure-dependent production of nitric oxide, and mitigated pressure-dependent and shear-dependent barrier failure. Lastly, the polymer was able to block bradykinin-induced increase in endothelial albumin permeability. The development of similar functionalized polymers for human use would represent a significant advance in resuscitation science. Certain illnesses and iatrogenic interventions can cause degradation of the EG. It is not known whether restitution of the EG promotes the survival of the patient. First trials that focus on the reorganization and/or restitution of the EG seem promising In conclusion, much more work is needed to develop therapies directed to exploit the multi-functional glycocalyx [56, 57].

20.8 ExtraCorporeal Membrane Oxygenation (ECMO) and Trauma

A blood pump is needed to push the venous blood through the capillaries of the oxygenator (a membrane oxygenator conceptually similar to the human lungs), which ensures the blood gas exchange (elimination of CO_2 and O_2 uptake).

ECMO can be considered for partial or full support in cases of potentially reversible post-traumatic cardiopulmonary failure. In trauma patients, no specific diagnoses are absolute indications or contraindications to ECMO therapy, *other than irreversible injury*.

Although in cardiac surgery, veno-arterial (VA) ECMO is often used to support the function of both the heart and lungs, in trauma patients, veno-venous (VV) ECMO is most commonly used to support acute respiratory distress syndrome (ARDS) or acute respiratory failure due to traumatic processes (although use of VA ECMO for post-traumatic shock states has also been described).

The recently published EOLIA (ECMO to Rescue Lung Injury in severe ARDS) trial of ECMO support for severe respiratory failure failed to demonstrate mortality reduction with the use of early ECMO. Nevertheless, substantial crossover between the control and ECMO arms yielded a significantly advantaged secondary outcome for the combined outcome of mortality and crossover. As such, the overall role of ECMO support remains controversial [58].

Thoracic trauma leading to pulmonary dysfunction is the most common indication for ECMO reported [59]. Acute respiratory failure (ARF) is multifactorial in trauma patients with diverse underlying pathophysiological mechanisms. In a blunt thoracic injury, all the chest compartments can be affected and are directly responsible for mortality of 20–25%. Two main mechanisms contribute to pulmonary injury: the first mechanism is a direct trauma leading to contusion, intra-alveolar hemorrhage, and aspiration pneumonia. The second mechanism is an indirect immunological lung injury, which may result from extrapulmonary trauma and/or the required management of trauma patients (massive transfusion, fluid overload, ventilator lung induced injury, etc.) leading to acute respiratory distress syndrome (ARDS). Extracorporeal membrane oxygenation (ECMO) is an attractive therapy in ARF. In 1972, the first successful use of ECMO was in a 24-year-old polytrauma patient who developed a "shock lung syndrome" [60]. Severe ARF requiring mechanical ventilation (MV) in trauma patients is associated with high mortality and increased hospital stay. In patients with severe impaired gas exchange despite optimized MV, ECMO is proposed to avoid injurious lung ventilation. It is prudent to start ECMO at an earlier stage to avoid irreversible MV-induced pulmonary injury in these cases. In severe thoracic trauma cases requiring lung resection or progressive lung fibrosis with severely limited reserve, ECMO may prove to be the main therapy as a bridge to lung transplant.

Among trauma patients with ARF, those with a traumatic brain injury represent a specific group as their prognosis is mainly dependent on neurological recovery. These patients may require earlier ECMO support compared with non-brain-injured patients, to prevent secondary neurological injury from severe hypoxemia,

hypercapnic acidosis, and worsening cerebral edema from fluid overload. The goal of ECMO is to support the patients who have good functional prognosis from their neurological injury. Unfortunately, this prognostication is not easy in brain-injured patients at the time when they are in need of ECMO.

When comparing ECMO and conventional therapy in the trauma population, there is a signal for improved outcomes using early ECMO. A recent propensity score-matched cohort study comparing ECMO versus conventional ventilator therapy demonstrated a survival advantage for ECMO [61]. With 17 patients in each arm, ECMO was associated with a significant survival advantage (65% vs. 24%, $p = 0.01$). However, there was a tradeoff in complications, with the ECMO group having more bleeding complications and the conventional group having more pulmonary complications.

Traditionally, trauma patients have been excluded from ECMO consideration due to a high bleeding risk. However, with improved ECMO circuit technology (newer pump systems, reduced circuit area, newer biocompatible circuit material, heparin coating, etc.), and a relatively high blood flow during veno-venous (VV) ECMO, thrombotic complications during heparin-free ECMO runs are relatively uncommon [62].

Further, many centers are continuously pushing the envelope to minimize anticoagulation ranges. In select cases, patients may be initiated on a heparin-free protocol for several days where there is a risk of ongoing hemorrhage. This may be especially true in the polytrauma patient who has both a severe traumatic brain injury and a severe ARDS.

Which method of ECMO, VV, or VA is more appropriate for trauma patients?

Mode of ECMO should be based on the patient disease process. Those with only respiratory failure or shock reasonably thought to be caused by severe hypoxia should be candidates for VV ECMO. Those with refractory cardiac dysfunction/cardiogenic shock should be placed on VA ECMO.

References

1. Hazeldine J, Hampson P, Lord JM. The diagnostic and prognostic value of systems biology research in major traumatic and thermal injury: a review. Burns Trauma. 2016;4(1):33.
2. Moore F, Moore E. Evolving concepts in the pathogenesis of postinjury multiple organ failure. Surg Clin North Am. 1995;75(2):257–77.
3. Sauaia A, Moore FA, Moore EE. Postinjury inflammation and organ dysfunction. Crit Care Clin. 2017;33(1):167–91. https://doi.org/10.1016/j.ccc.2016.08.006.
4. Hesselink L, Hoepelman RJ, Spijkerman R, de Groot MCH, van Wessem KJP, Koenderman L, Leenen LPH, Hietbrink F. Persistent Inflammation, Immunosuppression and Catabolism Syndrome (PICS) after polytrauma: a rare syndrome with major consequences. J Clin Med. 2020;9(1):191. https://doi.org/10.3390/jcm9010191. PMID: 31936748; PMCID: PMC7019692.
5. Hauschild DB, Oliveira LDA, Ventura JC, Farias MS, Barbosa E, Bresolin NL, Moreno YMF. Persistent inflammation, immunosuppression and catabolism syndrome (PICS) in critically ill children is associated with clinical outcomes: a prospective longitudinal study. J Hum Nutr Diet. 2021;34(2):365–73. https://doi.org/10.1111/jhn.12798. PMID: 32767403.

6. Patel JJ, Rosenthal MD, Miller KR, Martindale RG. The gut in trauma. Curr Opin Crit Care. 2016;22(4):339–46. https://doi.org/10.1097/mcc.0000000000000331.
7. Chen P. Gut microbiota and pathogenesis of organ injury. In: Advances in experimental medicine and biology. New York, NY: Springer; 2020. https://doi.org/10.1007/978-981-15-2385-4.
8. Howard BM, Kornblith LZ, Christie SA, Conroy AS, Nelson MF, Campion EM, et al. Characterizing the gut microbiome in trauma: significant changes in microbial diversity occur early after severe injury. Trauma Surg Acute Care Open. 2017;2(1):e000108. https://doi.org/10.1136/tsaco-2017-000108).
9. Armacki M, et al. Thirty-eight-negative kinase 1 mediates trauma-induced intestinal injury and multi-organ failure. J Clin Invest. 2018;128(11):5056–72.
10. Dickson RP, Singer BH, Newstead MW, Falkowski NR, Erb-Downward JR, Standiford TJ, et al. Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome. Nat Microbiol. 2016;1(10):16113.
11. Tan JY, Tang YC, Huang J. Gut microbiota and lung injury. Adv Exp Med Biol. 2020;1238:55–72. https://doi.org/10.1007/978-981-15-2385-4_5. PMID: 32323180.
12. Mukherjee S, Hanidziar D. More of the gut in the lung: how two microbiomes meet in ARDS. Yale J Biol Med. 2018;91(2):143–9.
13. Delano MJ, Ward PA. Sepsis-induced immune dysfunction: can immune therapies reduce mortality? J Clin Invest. 2016;126(1):23–31.
14. Sundman MH, Chen NK, Subbian V, Chou YH. The bidirectional gut-brain-microbiota axis as a potential nexus between traumatic brain injury, inflammation, and disease. Brain Behav Immun. 2017;66:31–44. https://doi.org/10.1016/j.bbi.2017.05.009. PMID: 28526435.
15. Li H, Sun J, Du J, Wang F, Fang R, Yu C, Xiong J, Chen W, Lu Z, Liu J. Clostridium butyricum exerts a neuroprotective effect in a mouse model of traumatic brain injury via the gut-brain axis. Neurogastroenterol Motil. 2018;30:e13260.
16. Tyler Patterson T, Grandhi R. Gut microbiota and neurologic diseases and injuries. Adv Exp Med Biol. 2020;1238:73–91. https://doi.org/10.1007/978-981-15-2385-4_6. PMID: 32323181.
17. Wallace DJ, Sayre NL, Patterson TT, Nicholson SE, Hilton D, Grandhi R. Spinal cord injury and the human microbiome: beyond the brain-gut axis. Neurosurg Focus. 2019;46(3):E11. https://doi.org/10.3171/2018.12.FOCUS18206. PMID: 30835680.
18. Zhu C, Grandhi R, Patterson T, Nicholson S. A review of traumatic brain injury and the gut microbiome: insights into novel mechanisms of secondary brain injury and promising targets for neuroprotection. Brain Sci. 2018;8(6):113. https://doi.org/10.3390/brainsci8060113.
19. Brenner LA, Stearns-Yoder KA, Hoffberg AS, Penzenik ME, Starosta AJ, Hernandez TD, Hadidi DA, Lowry CA. Growing literature but limited evidence: a systematic review regarding prebiotic and probiotic interventions for those with traumatic brain injury and/or posttraumatic stress disorder. Brain Behav Immun. 2017;65:57–67.
20. Benakis C, Brea D, Caballero S, Faraco G, Moore J, Murphy M, Sita G, Racchumi G, Ling L, Pamer EG, et al. Commensal microbiota affects ischemic stroke outcome by regulating intestinal gammadelta T cells. Nat Med. 2016;22:516–23.
21. Kigerl KA, Hall JC, Wang L, Mo X, Yu Z, Popovich PG. Gut dysbiosis impairs recovery after spinal cord injury. J Exp Med. 2016;213:2603–20.
22. Kigerl KA, Mostacada K, Popovich PG. Gut microbiota are disease-modifying factors after traumatic spinal cord injury. Neurotherapeutics. 2018;15(1):60–7. https://doi.org/10.1007/s13311-017-0583-2.
23. Kang W, Kudsk KA. Is there evidence that the gut contributes to mucosal immunity in humans? JPEN J Parenter Enteral Nutr. 2007;31(3):246–58.
24. Pu H, Doig GS, Heighes PT, Allingstrup MJ. Early enteral nutrition reduces mortality and improves other key outcomes in patients with major burn injury: a meta-analysis of randomized controlled trials. Crit Care Med. 2018;46(12):2036–42. https://doi.org/10.1097/CCM.0000000000003445. PMID: 30222632.

25. Lubbers T, de Haan JJ, Luyer MD, et al. Cholecystokinin/cholecystokinin-1receptor-mediated peripheral activation of the afferent vagus by enteral nutrients attenuates inflammation in rats. Ann Surg. 2010;252:376–82.
26. Cruzat V, Macedo Rogero M, Noel Keane K, Curi R, Newsholme P. Glutamine: metabolism and immune function, supplementation and clinical translation. Nutrients. 2018;10(11):1564. https://doi.org/10.3390/nu10111564. PMID: 30360490; PMCID: PMC6266414.
27. Peng Z, Ban K, LeBlanc A, Kozar RA. Intraluminal tranexamic acid inhibits intestinal sheddases and mitigates gut and lung injury and inflammation in a rodent model of hemorrhagic shock. J Trauma Acute Care Surg. 2016;81:358.
28. Xiao J, Peng Z, Liao Y, Sun H, Chen W, Chen X, Wei Z, Yang C, Nüssler AK, Liu J, Yang W. Organ transplantation and gut microbiota: current reviews and future challenges. Am J Transl Res. 2018;10(11):3330–44.
29. Keskey R, Cone JT, DeFazio JR, Alverdy JC. The use of fecal microbiota transplant in sepsis. Transl Res. 2020;226:12–25. https://doi.org/10.1016/j.trsl.2020.07.002. PMID: 32649987; PMCID: PMC7572598.
30. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for clostridium difficile infection: systematic review and metaanalysis. Am J Gastroenterol. 2013;108:500–8.
31. Sartelli M, Di Bella S, McFarland LV, Khanna S, Furuya-Kanamori L, Abuzeid N, et al. 2019 update of the WSES guidelines for management of Clostridioides (Clostridium) difficile infection in surgical patients. World J Emerg Surg. 2019;14(1):8. https://doi.org/10.1186/s13017-019-0228-3.
32. Vitko HA, Sekula LK, Schreiber MA. Probiotics for trauma patients: should we be taking a precautionary approach? J Trauma Nurs. 2017;24(1):46–52. https://doi.org/10.1097/JTN.0000000000000263. PMID: 28033143.
33. Rondanelli M, Faliva MA, Perna S, Giacosa A, Peroni G, Castellazzi AM. Using probiotics in clinical practice: where are we now? A review of existing meta-analyses. Gut Microbes. 2017;8(6):521–43. https://doi.org/10.1080/19490976.2017.1345414. PMID: 28640662; PMCID: PMC5730384.
34. Tan M, Zhu JC, Du J, Zhang LM, Yin HH. Effects of probiotics on serum levels of Th1/Th2 cytokine and clinical outcomes in severe traumatic brain-injured patients: a prospective randomized pilot study. Crit Care. 2011;15:R290.
35. Kotzampassi K, Giamarellos-Bourboulis EJ, Voudouris A, Kazamias P, Eleftheriadis E. Benefits of a synbiotic formula (Synbiotic 2000Forte®) in critically ill trauma patients: early results of a randomized controlled trial. World J Surg. 2006;30(10):1848–55.
36. Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, Beishuizen A, Briegel J, Carcillo J, Christ-Crain M, Cooper MS, Marik PE, Umberto Meduri G, Olsen KM, Rodgers S, Russell JA, Van den Berghe G. Correction to: Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Intensive Care Med. 2018;44(3):401–2. https://doi.org/10.1007/s00134-018-5071-6.
37. Marik PE, Pastores SM, Annane D, et al. American College of Critical Care Medicine. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med. 2008;36(6):1937–49.
38. Yao YM, Zhang H. Better therapy for combat injury. Mil Med Res. 2019;6(1):23. https://doi.org/10.1186/s40779-019-0214-9.
39. Van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. Crit Care Med. 2003;31(2):359–66.
40. Yamada T, Shojima N, Noma H, Yamauchi T, Kadowaki T. Glycemic control, mortality, and hypoglycemia in critically ill patients: a systematic review and network meta-analysis of randomized controlled trials. Intensive Care Med. 2017;43(1):1–15. https://doi.org/10.1007/s00134-016-4523-0. PMID: 27637719.

41. Finfer S, Chittock D, Li Y, et al. NICE-SUGAR Study Investigators for the Australian and New Zealand Intensive Care Society Clinical Trials Group and the Canadian Critical Care Trials Group. Intensive versus conventional glucose control in critically ill patients with traumatic brain injury: long-term follow-up of a subgroup of patients from the NICESUGAR study. Intensive Care Med. 2015;41:1037–47.
42. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345:1359–67.
43. Van den Berghe G, Schetz M, Vlasselaers D, et al. Clinical review: intensive insulin therapy in critically ill patients: NICE-SUGAR or Leuven blood glucose target? J Clin Endocrinol Metab. 2009;94:3163–70.
44. Richards JE, Scalea TM, Mazzeffi MA, Rock P, Galvagno SM Jr. Does lactate affect the association of early hyperglycemia and multiple organ failure in severely injured blunt trauma patients? Anesth Analg. 2018;126:904–10.
45. Régnier MA, Raux M, Le Manach Y, et al. Prognostic significance of blood lactate and lactate clearance in trauma patients. Anesthesiology. 2012;117:1276–88.
46. Bellomy ML, Freundlich RE. Hyperglycemia and elevated lactate in trauma: where do we go from here? Anesth Analg. 2018;126(3):748–9. https://doi.org/10.1213/ANE.0000000000002757.
47. Levy RM, Mollen KP, Prince JM, et al. Systemic inflammation and remote organ injury following trauma require HMGB1. Am J Phys Regul Integr Comp Phys. 2007;293:R1538.
48. Korff S, Loughran P, Cai C, Lee YS, Scott M, Billiar TR. Eritoran attenuates tissue damage and inflammation in hemorrhagic shock/trauma. J Surg Res. 2013;184(2):e17–25. https://doi.org/10.1016/j.jss.2013.03.023.
49. Thompson KB, Krispinsky LT, Stark RJ. Late immune consequences of combat trauma: a review of trauma-related immune dysfunction and potential therapies. Mil Med Res. 2019;6:11.
50. Li ZG, Scott MJ, Brzóska T, Sundd P, Li YH, Billiar TR, et al. Lung epithelial cell-derived IL-25 negatively regulates LPS-induced exosome release from macrophages. Mil Med Res. 2018;5:24.
51. Zhang H, Feng YW, Yao YM. Potential therapy strategy: targeting mitochondrial dysfunction in sepsis. Mil Med Res. 2018;5:41.
52. Timmermans K, Kox M, Vaneker M, van den Berg M, John A, van Laarhoven A, et al. Plasma levels of danger- associated molecular patterns are associated with immune suppression in trauma patients. Intensive Care Med. 2016;42:551–61. https://doi.org/10.1007/s00134-015-4205-3. PMID: 26912315.
53. Hazeldine J, Naumann DN, Toman E, Davies D, Bishop JRB, Su Z, Hampson P, Dinsdale RJ, Crombie N, Duggal NA, Harrison P, Belli A, Lord JM. Prehospital immune responses and development of multiple organ dysfunction syndrome following traumatic injury: a prospective cohort study. PLoS Med. 2017;14(7):e1002338. https://doi.org/10.1371/journal.pmed.1002338.
54. Giantsos KM, Kopeckova P, Dull RO. The use of an endothelium-targeted cationic copolymer to enhance the barrier function of lung capillary endothelial monolayers. Biomaterials. 2009;30(29):5885–91.
55. Giantsos-Adams K, Lopez-Quintero V, Kopeckova P, Kopecek J, Tarbell JM, Dull R. Study of the therapeutic benefit of cationic copolymer administration to vascular endothelium under mechanical stress. Biomaterials. 2011;32(1):288–94.
56. Jedlicka J, Becker BF, Chappell D. Endothelial glycocalyx. Crit Care Clin. 2020;36(2):217–32. https://doi.org/10.1016/j.ccc.2019.12.007. PMID: 32172810.
57. Cao RN, Tang L, Xia ZY, Xia R. Endothelial glycocalyx as a potential therapeutic target in organ injuries. Chin Med J. 2019;132(8):963–75. https://doi.org/10.1097/CM9.0000000000000177.
58. ClinicalTrails.gov. NCT01470703 Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA); 2016.
59. Zonies D, et al. AAST Critical Care Committee clinical consensus: ECMO, nutrition. Trauma Surg Acute Care Open. 2019;4:e000304. https://doi.org/10.1136/tsaco-2019-000304.

60. Hill JD, O'Brien TG, Murray JJ, Dontigny L, Bramson ML, Osborn JJ, Gerbode F. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung. N Engl J Med. 1972;286(12):629–6349.
61. Guirard D, Okoye O, Schmid B, et al. Venovenous extra-corporeal life support improves survival in adult trauma patients with acute hypoxemic respiratory failure: a multicenter retrospective cohort study. J Trauma Acute Care Surg. 2014;76:1275–81.
62. Zonies D. ECLS in trauma: practical application and a review of current status. World J Surg. 2017;41(5):1159–64. https://doi.org/10.1007/s00268-016-3586-y.