Lessons from the ICU
Under the Auspices of the European Society of Intensive Care Medicine
Series Editors: Maurizio Cecconi · Daniel De Backer

David Pérez-Torres
María Martínez-Martínez
Stefan J. Schaller *Editors*

Best 2022 Clinical Cases in Intensive Care Medicine

From the ESICM NEXT Committee Clinical Case Contest

Springer

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Lessons from the ICU is a Book Series published by Springer under the auspices of the *European Society of Intensive Care Medicine* (ESICM). The aim of the Series is to provide focused and state-of-the-art reviews of central topics in Intensive Care. Ultimately, its mission is to transfer the latest knowledge to the bedside in order to improve patient outcomes. Accordingly, the ESICM has also developed *Lessons from the ICU* with the vision or providing the best resources for everyone working in Intensive Care.

Each volume presents a comprehensive review of topical issues in Intensive Care. The volumes are intended to cover the majority of aspects that intensive care professionals are likely to encounter in the course of their career. Books offer an excellent guide for residents who are new to the ICU, and for allied professionals, senior consultants as well as nurses and allied healthcare professionals.

The chapters are organized in a way that allows the reader to quickly familiarize or reacquaint themselves with the pathophysiological background before moving on to diagnosis and treatment. Each chapter includes a list of Take Home Messages, as well as practical examples that apply theoretical knowledge in real clinical scenarios. Each volume in the Series is edited by international Key Opinion Leaders in Intensive Care, and each chapter is written by experts in the field.

In summary, this Series represents a valuable contribution to fill the gap in the current Intensive Care literature by providing top-quality literature reviews that can be easily digested and used at the bedside to improve patient outcomes.

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Foreword

As an intensivist with over 20 years of experience in intensive care medicine, I am privileged to introduce this outstanding collection of clinical cases written by junior intensivists from NEXT.

NEXT represents the younger generation of intensivists from ESICM, and they are the future of our community.

If their leadership matches this book's quality, our specialty's future will be very safe and bright, and our patients and families will receive better and better care.

The issues presented in this book provide an unparalleled insight into the challenges and complexities of intensive care medicine. In addition, the practical nature of the cases and the take-home messages they offer make this book an essential resource for anyone involved in the care of critically ill patients.

The authors of this book have put together a fantastic set of cases that cover a wide range of topics in intensive care medicine. The well-written cases provide a wealth of information on managing critically ill patients in different clinical scenarios. In addition, the possibilities are designed to challenge and inspire readers, providing them with a unique opportunity to learn from the experiences of others.

As a mentor to many junior intensivists, I know how difficult it can be to navigate the complexities of intensive care medicine. The cases presented in this book testify to the dedication and expertise of the junior intensivists who created them. The authors have done an outstanding job translating their experiences into actionable take-home messages that clinicians can apply at the bedside.

One of this book's strengths is how the authors have structured the cases. Each case starts with a detailed patient presentation description, including their medical history, physical exam findings, and laboratory results. This information is followed by a discussion of the differential diagnosis, highlighting the key features that distinguish one diagnosis from another.

The authors then describe their approach to managing the patient, including diagnostic tests, pharmacological agents, and other interventions. The authors also provide a detailed explanation of the rationale behind their decisions, which is a valuable insight into the thought process of experienced clinicians.

What I find particularly impressive about this book is how the authors have woven important take-home messages throughout each case. These messages are practical, evidence-based, and an excellent resource for clinicians at any career stage. In addition, the authors have done an outstanding job translating their experience into actionable insights that clinicians can apply to their practice.

I also appreciate how the authors have included cases covering a broad range of clinical scenarios. For example, there are cases of sepsis, acute respiratory distress syndrome, neurointensive care, renal failure, and many other topics. This diversity of patients is a testament to the broad range of expertise of the junior intensivists who created them.

In conclusion, I highly recommend this book to anyone involved in the care of intensive care patients. The cases presented in this book are practical and insightful and offer a unique opportunity to learn from the experiences of others. The take-home messages are evidence-based and provide clinicians with actionable insights

they can apply at the bedside. I am confident that this book will significantly contribute to intensive care medicine, and I look forward to seeing its impact on the practice of intensive care medicine.

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Preface

The NEXT Committee of the European Society of Intensive Care Medicine (ESICM) advocates for the interests and ambitions of young intensivists and trainees across Europe and internationally. The NEXT Committee is eager to receive feedback on how the Society can be improved to benefit the next generation of intensivists. All ESICM members under 37 years of age are per statutes considered NEXT members. Feel always free to contact your NEXT representatives and ask questions or support our initiatives (e.g., visual abstracts or quizzes on social media).

In 2022, the NEXT Committee organized a Clinical Case Contest to familiarize NEXT members with educational writing, even if they had little to no prior experience. To ensure the quality of the clinical cases, a fully certified intensivist supervised the content and provided a signed statement of responsibility. We received clinical cases from intensivists worldwide with varying specialty backgrounds and resources, resulting in a diverse representation of intensive care medicine. The two best cases were invited to present at LIVES 2022 as faculty, while the subsequent three best cases were invited as attendants.

Many of the cases submitted presented intriguing clinical scenarios worth reading, so we compiled them into a book thanks to the support of ESICM leadership and Springer publisher. The clinical cases underwent a review process to improve their content, allowing young intensivists and trainees to gain experience in the editorial process. Thus, "Lessons from the ICU: Best 2022 Clinical Cases in Intensive Care Medicine" was created.

The book is divided into six sections: severe infections and sepsis, respiratory medicine, cardiovascular medicine, neurocritical care and severe trauma, severe endocrine and metabolic disorders, and severe inflammatory disorders. Each section contains a set of clinical cases preceded by an introductory chapter providing an extensive overview of the diseases covered. This enables readers to enhance their knowledge from a fundamental theoretical background and learn the specifics of certain aspects of the disease through actual cases.

Each clinical case in the book has a didactic approach, including "Learning Objectives," "Take-Home Messages," and relevant "References." The clinical cases begin with a brief "Introduction" and "Case Presentation." Then, "Investigations," "Differential Diagnosis," and "Treatment" are presented. Afterwards, the "Evolution, Outcome, and Follow-Up" are described. Finally, the "Discussion" section discusses the clinical significance of the proposed case, including similar cases that have been published.

Although this textbook is not a replacement for appropriate training and experience, our hope is that it will enhance the learning experience of young physicians studying intensive care medicine and serve as a review for those who have completed their training.

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I The Best Clinical Cases in Severe Infections and Sepsis

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The Best Clinical Cases in Severe Infections and Sepsis

Contents

Principles and Management of Sepsis

Andreas Edel, Kristina Fuest, and George Karlis

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1

Learning Objectives

- Recognize the importance of sepsis in the Intensive Care Unit, particularly early recognition and treatment of septic shock and organ dysfunction.
- Describe the epidemiology and various clinical presentations that may lead to admission to the Intensive Care Unit.
- Outline the clinical manifestations of septic shock and the potential complications that may lead to organ failure.
- Understand the diagnostic workup for source control with rapid administration of antibiotics and surgical intervention when indicated.
- Summarize the major principles guiding the management of sepsis in the Intensive Care Unit, including the adequate hemodynamic treatment for macro- and microperfusion and supportive therapy options.

1.1 Introduction

According to the Surviving Sepsis Campaign guidelines 2021, sepsis represents a life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis and septic shock are major healthcare problems with high incidence and high mortality rates. It is of paramount importance to identify and treat promptly a septic patient in order to improve the outcome [1]. For clinical purposes, organ dysfunction can be represented by an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. Septic shock is a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater mortality risk than with sepsis alone [2].

1.1.1 Prevalence

It is estimated that sepsis affects over 30 million people per year, accounting for billions in health care related costs annually. The mortality rate of sepsis ranges from 10 to 50%. Survivors often suffer long-term physical, psychological, and cognitive disability. Sepsis is responsible for approximately one-third of all ICU (Intensive Care Unit) admissions worldwide [3]. Furthermore, recent studies report that it is present in more than 50% of adult hospitalizations ending in death or discharge to hospice. In two-thirds of these cases, sepsis was the immediate cause of death. Patients who die from sepsis tend to be older adults with multiple chronic comorbidities and recent hospitalizations [4].

1.1.2 Relevance and Importance

Sepsis is a serious global health care problem. However, while sepsis affects individuals of any sex and age, there are significant disparities in the burden of the disease. More vulnerable populations such as elderly people, individuals with underlying chronic conditions, the immunocompromised, as well as pregnant women and

neonates are disproportionately affected. Moreover, low- and middle-income countries have higher incidence and mortality rates [5]. The concept of sepsis has been part of medicine since the ancient times, but still, it remains a condition that continues to challenge our understanding and current practice. Mainly, as it has variable presentation, response to treatment, and it is unpredictable in its outcome. The priorities in the approach of the septic patient are summarized as follows [2]:

- Early recognition with prompt treatment initiation.
- Prevention and support of organ dysfunction.
- Source control with rapid administration of antibiotics and surgical intervention when indicated.

1.2 Definition

1.2.1 Evolution and History of Sepsis Definition

Definition and the term "sepsis" changed throughout history. First, described by Semmelweis and others as a systemic reaction to bacteria [6], the insights of sepsis became increasingly discovered. Knowing now that the devasting immune response of sepsis consists of pro- and anti-inflammatory pathways [7] reflecting the immune reaction to the pathogens and of the host [8]. The proinflammatory host reaction involves the activation of different defense systems potentially leading to a vicious circle. These activation processes involve leukocytes as well as the coagulation and complement system [7, 9]. Especially, material of the dead body cells, so called damage-associated molecular patters (DAMPs), continue to fuel this proinflammatory response [7]. On the other hand, the host tries to reduce this hyperimmune reaction by activating the anti-inflammatory pathways [10]. These pathways are driven by the neuroendocrine regulation system [11] as well as an impaired immune cell function [7]. All this leads to vasodilation, thrombosis, and finally impaired tissue perfusion with hypooxygenation causing organ dysfunction and, eventually, failure [7]. This organ dysfunction defines sepsis according to the third and latest definition of sepsis published in 2016 [2]. Still, the total complexity of sepsis is not reflected in the current sepsis definition. Therefore, ongoing research tries to phenotype sepsis according to the causative germs or with machine learning algorithms [12, 13]—this can be found below in the chapter "Future development and precision therapy options—new diagnostics."

1.3 Components of Sepsis Therapy

1.3.1 Sepsis Identification and Diagnostics

Every hour of an undiagnosed and subsequently untreated sepsis leads to a higher mortality. This connection could be shown by Seymour et al. in a retrospective study with about 50.000 patients, where 1-h delay led to an increased odds ratio 1.04 per

hour [95% CI (confidence interval), 1.02 to 1.05; $P < 0.001$] [14]. Taking this into account, a prompt identification of sepsis is crucial. Therefore, screening tools for a quick sepsis identification were developed. Since the third International Consensus Conference in 2016, the quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) was proposed to be a potentially easy and fast screening tool. But after six years of intensive research, the qSOFA demonstrated only a poor sensitivity leading to a recommendation against its use as a single screening tool for sepsis [1]. Other scores like the National Early Warning Score (NEWS) or the Modified Early Warning Score (MEWS) showed a better performance [15, 16]. Besides the sepsis screening, the search for the infectious source remains a principal component of the sepsis treatment. Here, only a detailed anamnesis and clinical examination help to reveal the potential infection source, whereas laboratory tests can only support and guide the clinical impression.

1.3.2 Basics of Sepsis Therapy: "Golden Hour of Sepsis"

Since sepsis is recognized as a medical emergency, the Surviving Sepsis Campaign (SCC) summarized the major diagnostic and therapeutic components in a "1-h bundle." This bundle includes prompt measurement of the lactate level, obtaining blood cultures for the microbiological diagnostic, initiation of an adequate antibiotic therapy, and an application of 30 mL/kg intravenous fluid bolus (if the mean arterial pressure is below 65 mmHg or the lactate level is above 2 mmol/L). In addition to an individualized fluid therapy, this treatment bundle also includes a differentiated catecholamine therapy [17].

The major underlying cause for organ failure is an impaired tissue perfusion. The major goal, therefore, is the maintenance of macro- and micro-perfusion. Macroperfusion is easily measured with the help of blood pressure, whereby higher mean arterial pressure level than 65 mmHg could not improve the patients' outcome [18]. Micro-perfusion instead is not easy to access, making lactate measurements as an auxiliary method to estimate the level of anaerobic metabolism necessary. The first therapeutic choice for improving tissue perfusion is a fluid application with preferred balanced crystalloids. Colloids like gelatin and starches, on the other hand, are not recommended because of their increased risk for acute kidney failure [19, 20], anaphylaxis [21], and mortality [22]. Albumin can be an additional therapeutic component, especially if high volumes of crystalloids are needed [1]. Since 2016, the SCC recommends a bolus of approximately 30 mL/kg intravenous crystalloids within 3 h [23]. In the current revised sepsis guideline, this recommendation is specified by the suggestion to use dynamic measurements like passive leg raising, stroke volume, stroke volume variation, and pulse pressure variation as well as echocardiography to adjust the initial fluid bolus to the actual individual need. Furthermore, the authors highlighted the capillary refill time as an easy bedside measurement in septic shock patients [1].

Adequate antibiotic therapy is another component of sepsis therapy. Considering that patients with septic shock had even higher mortality [24], Evans and colleagues now strongly recommend to initiate an empiric antibiotic therapy in all patients with

septic shock within 1 h. If the sepsis diagnosis is uncertain, other noninfectious causes should be ruled out first within 3 h before administering antibiotics. Besides anamnesis and clinical examination, this assessment can also include more time-consuming laboratory findings like procalcitonin (PCT) helping to distinguish between bacterial or viral infections [1]. Several studies have investigated its sensitivity and specificity with regard to identifying bacterial infection, so that a meta-analysis from 2013 with 3244 patients revealed a mean sensitivity of 0.77 (95% CI 0.72–0.81) and specificity of 0.79 (95% CI 0.74–0.84). Although laboratory parameters, like procalcitonin, are used to limit the possibility of infection, PCT-guided protocols for initiation antibiotic therapies could not show significant improvement of patients' outcomes [25, 26]. This is why the sole use of biomarkers for initiating an antibiotic therapy is not recommended [1].

The last component of the basic sepsis therapy is a rapid and adequate source control including removal of potential infected devices, drainage of abscesses, and surgical resection of infected tissues containing further contamination [27]. Prompt reaction is crucial, so a cluster of randomized trial in Germany could show that a delay of the source control per 1 h increased the mortality risk by 1% [28]. However, the ideal time for initiation of the source control remains unclear. Based only on small observational trials, a time frame of 6–12 h can be suggested [29–31]. To find the optimal intervention for addressing the infectious source, a multidisciplinary approach between radiology, interventional radiology, and surgery is necessary to illuminate and weigh all risks for the individual patient.

1.3.3 Treatment of Septic Shock

As septic shock is a combination of a decreased mean arterial pressure below 65 mmHg and an increased lactate level of above 2 mmol/L [2], this clinical constellation represents the most severe expression of sepsis, with a profound impairment of the cellular oxidative metabolism. Hereby, the lactate kinetics mirrors well the illness severity and the success of the ongoing treatment. Thus, a decreasing lactate level is associated with lower mortality, whereby repeated lactate measurements for treatment adjustments are necessary [32, 33]. As mentioned above, the initial fluid resuscitation therapy shall be flanked with dynamic parameters to individualize this treatment approach [1]. In cases where fluid therapy alone is not sufficient, norepinephrine as the first-line vasopressor shall be selected. Additionally, due to a "relative vasopressin deficiency" in septic shock [34, 35], the authors of the sepsis guidelines recommend vasopressin in case of a therapy-refractory septic shock defined by a norepinephrine dosage crossing a range of 0.25–0.5 μg/kg/min [1]. Based on results of the VANISH trial, vasopressin should be administered in fixed dose of 0.03 units/min to avoid severe side effects [1, 36]. Additionally, the application of corticosteroids is still suggested, whereas hydrocortisone has the best properties for shock reversal [37]. Despite this adequate therapy, further organs replacement therapies like renal replacement therapy, noninvasive or invasive ventilation, and even ECMO therapy may be required.

1.3.4 Additional Treatment Options: New Recommendations

In the last decade, several additional treatments strategies were discussed and investigated. One example is therapeutic application of vitamin C with its anti-inflammatory property. In 2017, a single center before–after study revealed a reduction mortality of septic patients if treated with a combination of vitamin C, hydrocortisone, and thiamine [38]. But this promising result of therapeutic vitamin C administration could neither be confirmed in randomized controlled trails (RCT) [39, 40] nor meta-analysis [41].

Another controversial treatment option for patients with sepsis is the blood purification method. This includes cytokine absorption devices like polymyxin B-immobilized polystyrene-derived fibers, used in the Polymyxin B hemoperfusion. Although a systematic review and meta-analysis from 2013 revealed a lower mortality for blood purification methods, the authors of the current sepsis guideline observed after correction of bias and study adjustment an even higher mortality with Polymyxin B hemoperfusion leading to a recommendation against it. But also, other blood purification methods like hemofiltration or plasma exchange remain controversial. Thus, the multicenter COMPACT-2 RCT with 115 septic shock patients evaluating the efficacy and safety of a high dose coupled plasma filtration and adsorption had to be stopped early due to a higher mortality in the intervention arm. Other research results favoring plasma exchange therapies [42] are still on primary research level and need still further trials.

1.4 Future Development and Precision Therapy Options—New Diagnostics

Sepsis as a syndrome is influenced by many factors and manifests itself in a wide variety of appearances, with the final pathway of organ failure. To be able to apply precision therapy options, it seems useful to phenotype or cluster patients into different risk categories at an early stage. It can be hypothesized "that such an approach will accelerate critical care research, leading to a richer understanding of the pathobiology of critical illness and of the key determinants of patient outcomes." [43] Besides the traditional classification based on the underlining pathogen, new efforts have been made to differentiate sepsis phenotypes according to their clinical presentation. A subdivision based on pathogens might be too simple since the different immunological responses remain not considered. However, the implementation of other classifications is complicated by the fact that immunological factors are not yet routinely measured. Out of three randomized control trials and three observational cohorts, Seymour et al. performed a machine-learning analysis using 29 routine parameters to cluster septic patients and found four phenotypes [12]. Here, patients differed in the extent of their organ dysfunctions, previous diseases, and inflammatory parameters. Interestingly, an increase of inflammatory biomarkers, like Interleukin-6 and Interleukin-10, was found only in two subgroups. The same was evident in terms of pro-coagulation parameters, which subsequently resulted in different mortality rates. In comparison to traditional classification, parameters like APACHE or SOFA score an overlap between the phenotypes was evident, indicating

a different subdivision than classical severity scores. Ma et al. also recognized the need of a further characterization based on routinely measured values in a cohort of 1.437 patients with septic shock [13]. Their aim was not only to identify subclasses of septic shock but also to find an optimal individualized treatment strategy for fluid and vasopressor application. After running a finite mixture and K-means clustering model, five subclasses were identified. Interestingly, similar structures as described above were recognized. Thus, a critical subclass with an impaired tissue perfusion and elevated lactate concentration was found, which could be compared with one phenotype of Seymour et al. Furthermore, a renal and a respiratory dysfunction subclass were described.

1.4.1 New Ways of Characterizing Sepsis: From Transcriptome to Precise Medical Therapy

Also, genes arrays can enrich the understanding and classification possibilities of sepsis. In the last decade, the technical improvement of sequencing a large amount of RNA simultaneously opened the possibility of analyzing thousands of transcripts of specific genes. Wong et al. could differentiate two different phenotypes of septic shock in their patient cohort of 168 pediatric patients by using computer-assisted image analysis and microarray-based reference mosaics [44]. They verified these results in a prospective cohort as well. One of the identified subclasses was characterized by a decreased expression of a specific gene pattern. These patients had an increased risk of mortality, if corticosteroids were prescribed (OR 4.1; CI, 1.4–12.0; $p = 0.011$) [44]. These findings were further supported by a post hoc analysis of the "VANISH" trial, a study comparing vasopressin and norepinephrine in the initial therapy phase of septic shock. After running gene expression profiling in that trial two transcriptomic response signatures were found. These two subclasses also had different reactions towards additional hydrocortisone application. The patients with a more immunocompetent profile had an increased mortality, if hydrocortisone was applied [45]. These results must be verified in a prospective study setting but these findings underline the importance of individualized precise medicine in future research.

1.4.2 New eHealth Strategies

"WHO defines eHealth as the cost-effective and secure use of information and communications technologies in support of health and health-related fields, including health-care services, health surveillance, health literature, and health education, knowledge and research" [46]. Hereby eHealth can include different components, like audio-video connection to transfer knowledge and expertise or machine learning algorithms being a new potential prediction tools for sepsis [47].

First steps were done in five US-Americans hospital in 2011, where a telemedicine approach with a multiprofessional team assessing compliance and reviewing the data was established [48]. In the meantime, retrospective and prospective observational telemedicine studies in either emergency departments or ICUs with audio-video con-

sulting system and additional decision support systems were published pointing to increased sepsis bundle compliance [49, 50] and to a decreased mortality [51–54]. These results are also supported by a German stepped-wedge cluster randomized controlled trial of Marx and colleagues showing an increased sepsis guideline adherence, too [55]. These approaches are now further developed, like in the Cleveland Clinic (USA), to an eHealth platform including not only audio-video components but also a complex system including telemetry, access to electronic health records, and electronic risk and decision support systems [56]. This concept represents the future of tele-health systems, which has to be still verified in an upcoming multicenter comparative effectiveness study [57].

1.4.3 New Diagnostic Approaches

1.4.3.1 Next-Generation Sequencing (NGS)

Although the gold standard for detection of fungal and bacterial germs is still the culture growth, next-generation sequencing has become increasingly available in the last years. Next-generation sequencing is a culture-independent PCR-based method detecting cell-free microbial DNA. Compared to traditional blood cultures, NGS has the advantage of a faster detection in hours [58]. In a small study of 50 patients with septic shock and 20 control patients without an infection undergoing elective surgery, NGS had a higher positive rate than traditional blood cultures (72% vs. 33%) at sepsis onset [59].

1.4.3.2 The Transcriptome of White Blood Cells

A promising early sepsis detection method is not based on the detection of a pathogen but searching for special gene expression signatures of circulating leukocytes. This analysis is based on the new-generation sequencing technology but instead of DNA, RNA is sequenced. This transcripted RNA reflects the host gene expression and is also called "transcriptome" [60]. This gene expression was analyzed in acute infection, and special expression signatures were found [61]. First, studies were able to distinguish between sepsis and noninfectious systemic inflammation [62, 63].

1.5 Follow-up Programs for Post-Sepsis Patients

Sepsis is not only associated with injuries during the ICU treatment but also after discharge. Cognitive and functional impairment as well as decrement in quality of life can be found in patients surviving sepsis [64–66]. Therefore, the current sepsis guideline suggests assessment and follow-up programs after discharge. Here, the screening of the not only sepsis specific post-intensive care syndrome (PICS) can be reasonable tool to detect deficiencies because PICS includes impairment of mental and subjective health as well as cognition and physical functional. PICS assessment, as described by Spies et al., contains a short PICS screening as well as an additional extended assessment if the initial PICS screening was tested positive [67]. Due to the imprecise evidence regarding the benefit of such follow-up services [68], further studies are ongoing, but their results are still pending [69, 70].

Take-Home-Message

- Sepsis and septic shock are major healthcare problems with high incidence and high mortality rates. It is of paramount importance to identify and treat promptly a septic patient in order to improve the outcome.
- The treatment of sepsis requires timely and aggressive intervention to improve patient outcomes. Here, one key aspect is the "1-h bundle" of actions that should be initiated within 1 h of recognizing the signs and symptoms of sepsis. These include obtaining blood cultures to identify the causative organism, starting intravenous antibiotics to treat the infection, and administering fluids to improve perfusion. The last component of the basic sepsis therapy is a rapid and adequate source control, including removal of potential infected devices, drainage of abscesses, and surgical resection of infected tissues containing further contamination.
- There is ongoing research to identify new and improved treatments for sepsis, with a particular focus on targeted therapies that address the underlying pathophysiology of the condition. Here, phenotyping to identify specific subtypes of sepsis and patient characteristics to tailor treatment accordingly is of special research interest.

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Infection in an Immunocompromised Patient, the Perfect Costume in Which to Hide

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Contents

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Learning Objectives

- Highlight the importance of the differential diagnosis of complications in severe immunocompromised patients.
- To learn about the antibiotic stewardship in a patient with AIDS admitted to the ICU.
- To be aware of the potential side effects of treatment and how to deal with them in a critical ill patient.
- To deal with the fragility and specific difficulties of intensive treatment of an immunocompromised patient in ICU.

2.1 Introduction

Human immunodeficiency virus (HIV) infection is a health care issue, with a global prevalence up to 37 million. There is still a high HIV-related mortality, especially in those patients with advanced-stage infections. With the development of new treatments with less adverse events, progression of patients to acquired immunodeficiency syndrome (AIDS) stage has decreased in the past decades. Nevertheless, 21.3% of patients diagnosed in 2016 in the United States (US) were already in this advanced stage [1]. Up to 10% of all HIV-infected hospitalized patients require admission to the Intensive Care Unit (ICU), mainly due to HIV-related infections, complications of antiretroviral treatment (ART), and also HIV-unrelated diseases [2].

With this case, we aim to point out the relevance of an extended differential diagnosis of the medical complications in a critically ill immunocompromised patient, such as those with AIDS-stage HIV infection.

Case Presentation

A 61 years-old male, former smoker, recently discharged from hospital after 9 days of stay due to a *Pneumocystis jirovecii* pneumonia (PCP), and consequently diagnosed of HIV in AIDS stage. He had 6 CD4+ cells/mm^3 and a viral load of 1,350,000/mm^3. Trimethoprim/sulfamethoxazole (TMP/SMX) 320/1600 mg three times a day plus steroids on tapering dose were started, as well as ART with bictegravir/emtricitabine/tenofovir alafenamide 50/25/200 mg once a day, being discharged after 9 days of admission.

Three days after finishing steroid treatment and 8 days after discharge, under correct TMP/SMX treatment, the patient developed new fever, and he consulted to the Emergency Department. On arrival, he was eupneic, with no respiratory insufficiency, mild hypotension (blood pressure of 88/56 mmHg, mean arterial pressure of 67 mmHg) without hypoperfusion signs, and afebrile. Physical examination showed preserved status, with mild rhonchi limited to the right hemithorax on pulmonary auscultation with no other relevant findings. Chest X-ray showed worsening of previous bilateral infiltrates. Main results on blood tests were C-reactive protein of 19 mg/dL (normal range (NR) less than 1 mg/dL), lactate dehydrogenase of 353 U/L (NR less than 234 U/L), and

lymphocyte count of 100/mm^3 (NR 900–4500/mm^3). Same dose of TMP/SMX, 40 mg of methylprednisolone twice a day and empiric treatment with ertapenem 1 g once a day and anidulafungin 200 mg followed by 100 mg once a day was started, and patient was readmitted to the hospital.

Once in the medical ward, high-resolution thorax computed tomography (CT) was performed showing bilateral infiltrates, with signs of organizing pneumonia (Fig. 2.1). Bronchoscopy was performed and showed a quantitative decrease in *Pneumocystis* cysts in the bronchoalveolar lavage (BAL). During the hospital stay, the microbiologist reported the isolation of *Mycobacterium avium intracelulare* (MAI) in a sputum culture from the previous admission, and treatment with azithromycin 500 mg once a day, rifampicin 600 mg once a day, ethambutol 800 mg once a day, and levofloxacin 500 mg once a day was added.

After four days, the patient developed rapid respiratory worsening. He showed an increased respiratory rate and respiratory effort, needing a non-rebreather mask. Arterial blood gas (ABG) showed pH 7.44, pCO_2 27.1 mmHg, and pO_2 98.7 mmHg; PaO_2/FiO_2 ratio was 99. He was transferred to the ICU to start high-flow nasal cannula therapy (HFNC) with 65% FiO_2 and 45 L per minute.

The initial diagnosis was acute respiratory distress syndrome due to MAI untreated infection and persistence of PCP, in context of immune reconstitution inflammatory syndrome, in a severe immunocompromised patient after recent ART initiation. Treatment with TMP/SMX, high-dose steroids, azithromycin, rifampicin, ethambutol, and levofloxacin was continued. However, the patient was persistently febrile and progressive respiratory worsening was observed, needing intubation and mechanical ventilation. The patient required a low-moderate dose of norepinephrine infusion (0.3 μcg/kg/min) mainly because of sedation. Initial mechanical ventilation settings were volume-controlled mode with protective lung ventilation: tidal volume 300 mL (5 mL/kg of predicted body weight), 28 breaths per minute, positive end-expiratory pressure (PEEP) of 14 cmH_2O, and

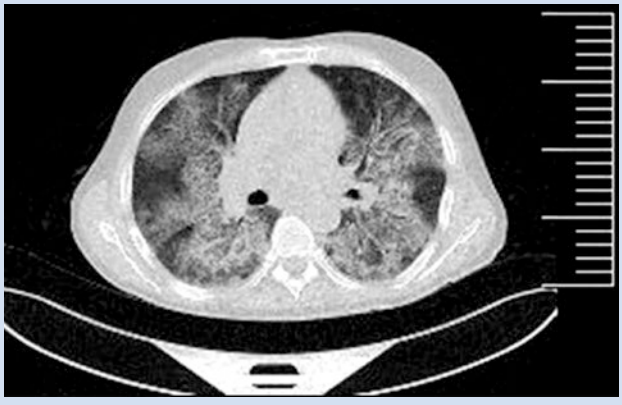

Fig. 2.1 High-resolution thorax CT showing extensive opacities in ground glass and some consolidative foci with bilateral perihilar septal thickenings with a "crazy paving" pattern

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FiO_2 50%, with plateau pressure of 30 cmH20. ABG showed a permissive hypercapnia (pH 7.30, pCO_2 55) and pO_2 of 104 mmHg, which led to decrease in FiO_2. The clinical team decided to perform another high-resolution thorax CT that showed stable bilateral infiltrates but with a mild increase of organizing pneumonia signs. At this point, bronchoscopy was performed again, resulting in a polymerase chain reaction (PCR) test positive for cytomegalovirus (CMV) (viral load 432 UI/mL) in BAL with no macroscopic relevant findings. That results were coincident with serum CMV PCR (viral load 1500 UI/mL). It was decided to start foscarnet 4500 mg twice a day instead of ganciclovir because of persistent pancytopenia, but the patient remained feverish without any other microbiological findings. After 20 days from ICU admission, sudden anisocoria was found on the physical examination, and two tonic-clonic seizures were observed.

2.2 Investigations

Cranial CT: Hypodensities in both corona radiata, a subacute hyperdensity on right parietal lobe, and a nodular hyperdensity on left parietal lobe.

Blood cultures: 15 blood cultures repeatedly negative.

Cerebrospinal fluid (CSF) analysis: Hyperproteinorrhachia with no pleocytosis and no hypoglycorrhachia. PCR was positive for herpes virus 8 and negative for the rest of microorganisms tested (*E. coli* K1, *L. monocytogenes*, *H. influenzae*, *N. meningitis*, *S. pneumoniae*, *S. agalactiae*, CMV, herpes simplex virus 1, herpes simplex virus 2, human herpes virus 6, varicella-zoster virus, JC virus, and *Cryptococcus neoformans*). CSF culture and bacilloscopy were negatives. CSF cytology showed mild inflammatory infiltrate compound by lymphocytes and polymorphonuclear leukocytes, with no atypical cells.

Electroencephalogram: Beta activity and diffuse delta slowing, without asymmetries or epileptiform activity.

Cranial magnetic resonance imaging (MRI) (Fig. 2.2): Cortical and juxtacortical multiple lessons on cerebellum, parietal, frontal, occipital, and posterior temporal lobes, with contrast-enhancing focus and microbleeding signs, and a more extensive lesion on right parietal lobe with gyral enhancement, compatible with cerebritis.

Transesophageal echocardiography: Mitral vegetations (up to 5 × 8 mm size) and aortic vegetation, with mild mitral and aortic regurgitation. No ventricular dysfunction, no pericardial effusion.

Beta-d-glucan (BDG) assay: Positive (NR < 2.9 pg/mL): 582.8 (day 1), 330.2 (day 4), 346 (day 8), 128.2 (day 16),101.1 (day 21), 61.2 pg/mL (day 28).

Aspergillus galactomannan antigen: Negative on serum and BAL.

Positron emission tomography (PET) scan: Diffuse pulmonary hypermetabolism and focal hypermetabolism on *gluteus maximus* muscle.

***Gluteus maximus* muscle biopsy**: Negatives culture, bacterial 16S rRNA sequencing, and fungal 18S rRNA sequencing. Cytology negative for malignance.

Atypical bacteria serologies: Negative for *Chlamydia*, *Coxiella,* and *Brucella*.

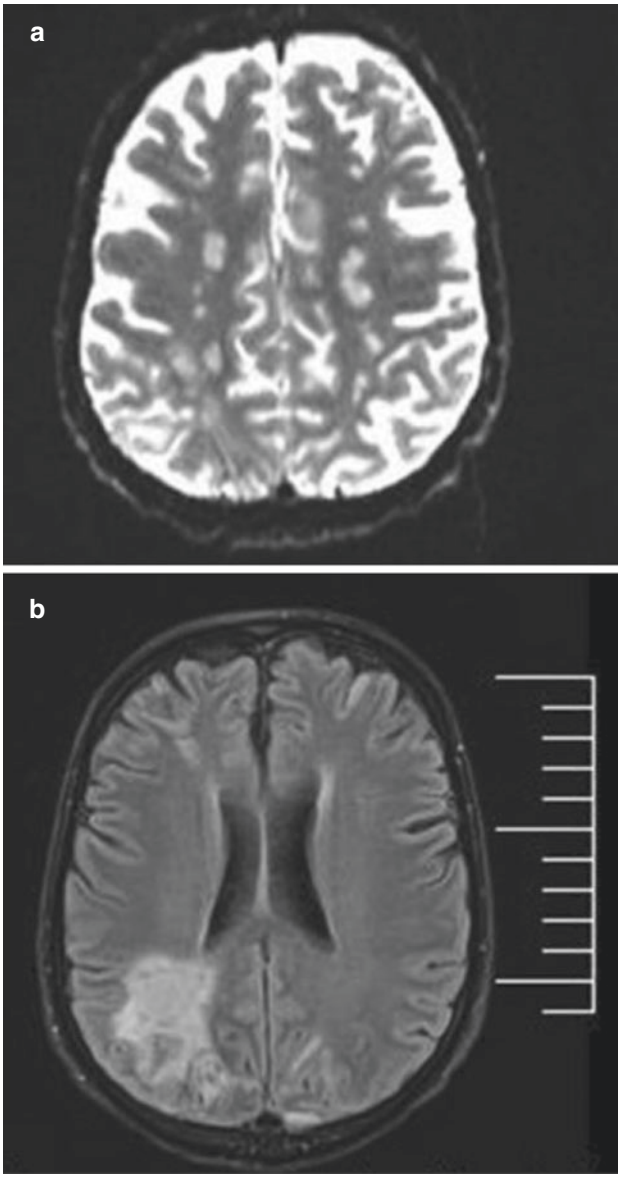

Fig. 2.2 **a** Diffusion-weighted magnetic (DWI) MRI sequence showing multiple cortical and juxtacortical ischemic lessons. **b** Fluid-attenuated inversion recovery (FLAIR) MRI sequence showing an extensive lesson on right parietal lobe with gyral enhancement

2.3 Differential Diagnosis

Fungal endocarditis.
Bacterial endocarditis (HACEK group bacteria).
MAI endocarditis.
Marantic endocarditis.

2.4 Treatment

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2.4.1 Nonpharmacological Treatment

Mechanical ventilation on volume-controlled mode with a permissive hypercapnia strategy because of high inspiratory and plateau pressures. Maximum FiO_2 50%.

2.4.2 Pharmacological Treatment

Neurological: Sedoanalgesia with remifentanil (maximum dose 0.533 mcg/kg/min) and propofol (maximum dose 3.2 mg/kg/h). Neuromuscular blockade with cisatracurium (maximum dose 5.9 mcg/kg/h). Antiepileptic treatment with levetiracetam 1000 mg twice a day.

Cardiovascular: Low-dose norepinephrine (less than 0.1 mcg/kg/min), which was withdrawn once sedoanalgesia was tapered.

Renal: Intravenous furosemide up to 60 mg/day to reach neutral balance.

Digestive/nutritional: Full-dose enteral nutrition with protein supplementation; occasional need for prokinetic treatment because of low gastric emptying.

Infectious: Endocarditis empiric treatment with meropenem 1 g three times a day, doxycycline 100 mg twice a day, teicoplanin 400 mg 3 doses separated by 12 h followed 400 mg once a day, and anidulafungin 200 mg followed by 100 mg once a day. Antiviral treatment switch from foscarnet to ganciclovir 5 mg/kg twice a day to include herpes virus 8 coverage and ART switch from Bictegravir/emtricitabine/tenofovir alafenamide to dolutegravir/emtricitabine/tenofovir disoproxil 50/200/245 mg once a day in order to avoid pharmacological interactions. Methylprednisolone was progressively tapered to 20 mg once a day. TMP/SMX for PCP and azithromycin, rifampicin, ethambutol, and levofloxacin for MAI infection stayed without changes.

2.5 Evolution, Outcome, and Follow-up

Because of cranial CT findings and persistent fever, endocarditis was suspected and transesophageal cardiac ultrasound showed vegetations on both mitral and aortic valves with mild valvular regurgitation. Broad-spectrum antibiotic treatment was initiated including anidulafungin due to a high-titer positive BDG test. Up to 15 blood cultures were extracted with negative results, and *Chlamydia*, *Coxiella,* and *Brucella* serologies were negative. PET scan showed diffuse pulmonary hypermetabolism and focal hypermetabolism on *gluteus maximus* muscle, therefore muscle biopsy was performed. It showed a negative result on cultures, bacterial 16S rRNA sequencing, and fungal 18S rRNA sequencing, with unspecific inflammatory infiltrate on the anatomopathology study.

Because of the absence of microbiological findings in repeated blood cultures and the decrease on BDG titers on subsequent tests, AIDS-related noninfective endocarditis was diagnosed. Anidulafungin and broad-spectrum antibiotic treatment were withdrawn and therapeutic TMP/SMX was changed to prophylactic dosage (160/800 mg three times a week) when negative galactomannan test was obtained and no hyphae were found at bronchoalveolar lavage.

After two weeks, the patient developed a clinical improvement that led to the sedation withdrawal and to pass to HFNC as respiratory support. Once awaken, physical examination showed persistent anisocoria and severe symmetric myopathy without other neurological focality.

Rehabilitation was initiated, and silver tracheostomy cannula was able to get occluded. Finally, after 73 days since the admission to the ICU, the patient was discharged to the medical ward to continue the treatment. Once on medical ward, nosocomial COVID-19 infection was detected, and the patient rapidly developed clinical worsening. In consensus with his family, the medical team decided to withhold life-sustaining measures, and finally the patient died 5 months after the hospital admission because of respiratory failure.

2.6 Discussion

The incidence of infective endocarditis (IE) has risen in HIV-infected patients and is associated with a high mortality [3]. Noninfective endocarditis (NIE), also known as nonbacterial thrombotic endocarditis or marantic endocarditis, is a rare condition associated with inflammatory and hypercoagulable states such as malignancy, autoimmune diseases, and HIV infection [4]. Berlot et al. described an incidence of 1% of NIE in ICU population [5]. Systemic embolism is the main manifestation, being cerebral emboli such as those we saw in our case the least common.

Diagnostic work-up requires excluding infective endocarditis, including atypical organisms. That require serial negative blood cultures (the number of negative blood cultures rose up to 15 in our case), atypical serologies, and even molecular tests on tissue [4], such as the bacterial 16S rRNA and the fungal 18S rRNA sequencing we performed on *gluteus maximus* muscle tissue. Our patient's clinical status did not allow to perform a mitro-aortic vegetation biopsy.

As a new diagnostic technique on bloodstream infections, beta-D-glucan assay seems to be reliable as an aid to early diagnosis of candidemia and allows a prompt start of antifungal treatment. However, due to the existence of false positives, its result should be interpreted cautiously and be supported by another diagnostic test [6].

In conclusion, a structured diagnostic work-up and a prompt response against acute infections are important for the ICU clinicians, especially when dealing with severely immunocompromised patients such as AIDS-stage HIV-infected patients.

Take-Home Messages

- Taking into account of host susceptibility, a structured diagnostic work-up could help diagnose opportunistic infections in the critically ill HIV-infected patient.
- Noninfective endocarditis (NIE) is an exclusion diagnosis that requires serial negative blood cultures, negative serology for atypical microorganisms, and even molecular test on tissue to rule out unusual causes of IE.
- Indirect tests such as beta-D-glucan assay could help in the early diagnosis of invasive fungal infections, but it should not exclusively guide the treatment.

Summary

A 61-year-old male, recently diagnosed with HIV infection in AIDS stage due to a *Pneumocystis jirovecii* pneumonia (PCP), reconsulted because of fever. Worsening of previous bilateral infiltrates on chest X-ray and inflammatory signs on blood test were observed. With the suspicion of PCP relapse, steroids were restarted, as well as empiric antibiotic and antifungal treatment.

A quantitative decrease of *Pneumocystis* cysts on BAL was found, but *Mycobacterium avium intracelulare* was identified in a sputum culture from the first admission, therefore specific treatment was started. Nevertheless, the patient developed a respiratory worsening that led him to ICU admission under invasive mechanical ventilation. Positive PCR test for cytomegalovirus in BAL and serum was detected, thus foscarnet was initiated. However, he remained feverish and sudden anisocoria and seizures appeared. Cranial CT scan showed multiple ischemic injuries; therefore, with the endocarditis suspicion, transesophageal cardiac ultrasound was performed showing mitro-aortic vegetations. Antibiotherapy was initiated, as well as antifungal treatment because of positive beta-d-glucan (BDG) assay, being both stopped after repeatedly negative blood cultures and a decrease on BDG levels, with the noninfective endocarditis diagnosis.

TMP/SMX was reduced to prophylactic dosing after negative galactomannan test was obtained and hyphae presence in BAL was excluded. Rehabilitation was initiated, and silver tracheostomy cannula was successfully occluded. Finally, the patient was discharged to the medical ward to continue the treatment, where he finally died 5 months after the hospital admission due to nosocomial COVID-19 infection.

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Intraabdominal Sepsis: Portal and Mesenteric Vein Thrombosis as First Presentation of Myeloproliferative Disease in a Young Woman

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Contents

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Learning Objectives

- Consider procoagulant states in patients with abdominal thrombosis and no risk factors for hepatopathies or malignancies.
- Increase awareness of the complexity associated with portal vein thrombosis among the medical community.
- Management of splanchnic vein thrombosis and prehepatic hypertension with discussion of the benefits and risks of anticoagulant medications.
- The importance of continuous reassessment of patients without making judgment based on previous information to avoid potentially dangerous anchoring biases.

3.1 Introduction

Portal vein thrombosis (PVT) is a condition, usually associated with hepatic cirrhosis or hypercoagulable syndromes, in which thrombi are formed within portal venous system and can extend to intrahepatic portal vein branches or to splenic and superior mesenteric veins, but it is only rarely recognized in otherwise healthy patients [1]. Many local and systemic factors, including intra-abdominal inflammation, liver tumors or cirrhosis, viral infections, congenital or acquired prothrombotic mutations, and myeloproliferative disorders, can be associated with splanchnic venous system thrombosis (SVT). We present a case of a 42-year-old lady, whose medical history was unremarkable, who has recently come to our attention for fever, ascites, abdominal pain, and hepatosplenomegaly associated with undiagnosed splanchnic venous thrombosis that evolved to intestinal perforation and septic shock. This case shows how misleading clinical presentation of a relatively uncommon disorder has determined delay in the diagnosis and therefore has led to an extremely severe septic shock sustained by multiresistant germs.

Case Presentation

A 42-year-old white Caucasian woman presented to our Emergency Department (ED) with fever up to 39 °C and abdominal pain. Her previous medical history was unremarkable, except for microcytic anemia, Gilbert disease, and previous *Epstein Barr Virus* (EBV) infection in February 2022. She was also vaccinated against *SARS-CoV2* with two jabs, the last administered in December 2021. Two days before ED admission, the patient got an abdomen computed tomography (CT) scan prescribed by her gynecologist because he detected free fluid in the Douglas pouch and high levels of CA-125 during a routine gynecological examination. The CT scan did not show any findings suggestive of genital malignancy but revealed instead a mild chronic hepatopathy with ascites and splenomegaly. On admission to the ED, the patient was febrile (38.5 °C), hemodynamically stable, GCS 15, mild pain on deep and superficial abdomen palpation. Blood specimens for generic blood tests and culture were withdrawn and sent to the laboratory. Results are reported in Table 3.1.

She was therefore admitted to the Internal Medicine ward and antibiotic therapy with piperacillin/tazobactam was

Table 3.1 Laboratory tests results on admission to Emergency Department and ICU

	Admission to Emergency Depatment	ICU admission	Reference values
Red blood cells (×10^12/L)	5.38	3.26	4.5–5.5
Hemoglobin (g/dL)	12.9	8.4	12.0–15.0
Hematocrit (%)	40.1	25.8	36–46
MCV (mean corpuscular volume, fL)	74.6	79.1	83–101
MCH (mean corpuscular hemoglobin, pg)	23.9	25.9	27–32
White blood cells (×10^9/L)	30.03	17.4	4.0–10.0
N% (neutrophils)	90.2	87	40–80
L% (lymphocytes)	4.2	8.7	20–40
M% (monocytes)	5.3	3.7	2–10
E% (eosinophils)	0.2	0.1	0.0–5.4
B% (basophils)	0.2	0.5	0.0–1.2
Platelets (×10^9/L)	434	348	150–450
Glycemia (mg/dL)	127	106	65–100
BUN (mg/dL)	10	31	10–23
Creatinine (mg/dL)	0.54	1.28	0.5–1.0
Sodium (mmol/L)	128	140	135–145
Potassium (mmol/L)	4.2	4.5	3.5–5.0
Calcium (mg/dL)	9.6	8.4	8.7–10.3
Total bilirubin (mg/dL)	3.3	1.3	0.3–1.2
Direct bilirubin (mg/dL)	1.2	0.9	<0.3
GOT (glutamic oxaloacetic transaminase, UI/L)	20	46	<35
GPT (glutamic pyruvic transaminase, UI/L)	21	12	<40
Alkaline phosphatase (UI/L)	126	106	46–116
GGT (gamma-glutamyl transferase, UI/L)	32	59	<38
Amylase (UI/L)	27	—	1–225
Lipase (UI/L)	22	—	0–50
INR (international normalized ratio)	1.22	2.48	0.8–1.2

(continued)

Table 3.1 (continued)

	Admission to Emergency Depatment	ICU admission	Reference values
a–PTT (activated partial thromboplastin, sec)	38.1	90.1	28–38
Fibrinogen (mg/dL)	492	390	200–400
D dimer (ng/mL)	—	13883	<500
Reactive C protein (mg/L)	71.3	94.2	<5–10
Procalcitonin (ng/mL)	—	>75	<0.05

started empirically. On the third day of hospitalization, her white blood cells (WBC) count increased, and a new CT scan showed complete thrombosis of the portal vein, partial recent thrombosis of the splenic vein, and severe distension of intestinal loops (Fig. 3.1). The patient was therefore started on enoxaparin, parenteral nutrition, and diuretics. Afterwards, the patient's clinical condition progressively deteriorated since she developed bilateral pleural effusion with progressive hypoxemic respiratory failure and severe diarrhea that led to hemodynamic instability and Intensive Care Unit (ICU) admission for severe hypovolemic shock.

She underwent emergency laparotomy with drainage of six liters of peritoneal fluid, bowel manipulation with lysis of adherences and section of a necrotic, perforated, intestinal loop. Because of the severe inflammation and massive bleeding, abdomen was temporarily closed with a Bogota-bag and, after two abdominal cavity revisions for bleeding control, vacuum-assisted abdominal closure was adopted. After surgery, the patient's condition was still critical, and she remained on high-dose vasopressors (noradrenaline and terlipressin) and put on antibiotic therapy with vancomycin, meropenem, and caspofungin. Progressively, the patient's condition improved and after five days of ICU stay, she was successfully weaned off mechanical ventilation and put on high flow nasal cannula. Abdominal cavity revisions were therefore performed after 48 and 96 h and during the last surgery for abdominal wall closure, hepatic biopsy was obtained. Meanwhile, our Hematology consultant recommended the following laboratory and genetic tests: reticulocytes count, schistocytes count, FVIII and FVIII inhibitors, C and S proteins, LAC (lupus anticoagulant), JAK2 (Janus Kinase 2), c-mpl (thrombopoietin receptor), CALR (calreticulin), and PNH (paroxysmal nocturnal hemoglobinuria) clone.

Blood cultures at ICU admission resulted positive for *Candida glabrata* and *Vancomycin-Resistant Enterococcus faecium*, and antimicrobial therapy was therefore modified with tedizolid instead of vancomycin. A peritoneal sample also tested positive for *E. faecium* XDR (extensively drug resistant) and so tigecycline was added to antimicrobial therapy. She progressively recovered from septic shock and, after sixteen days, was discharged from ICU and admitted to the Gastroenterology Department.

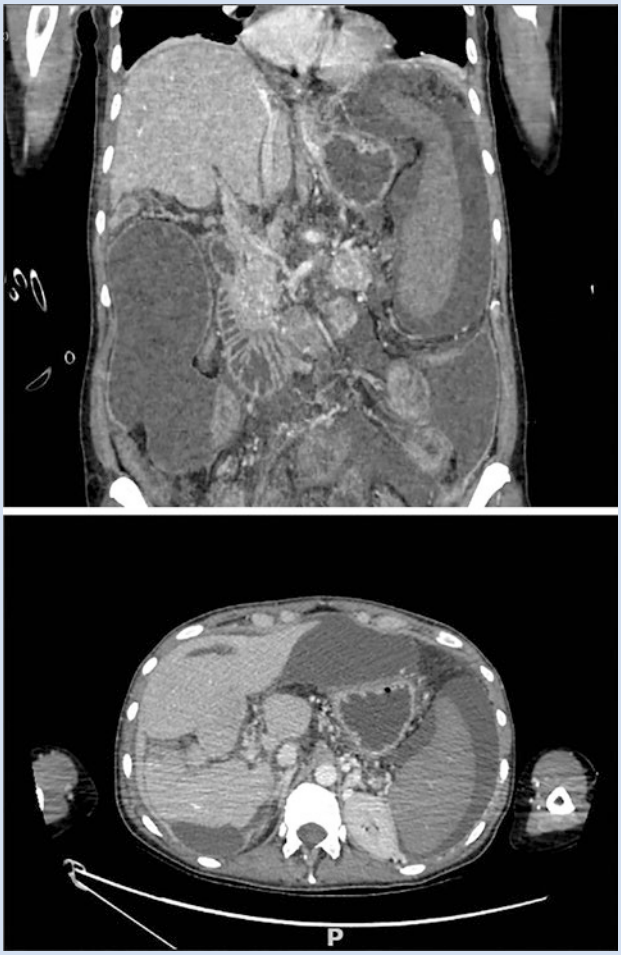

Fig. 3.1 Contrast-enhanced CT scan (late portal phase) showing splanchnic thrombosis

3.2 Investigations

PVT in healthy patients is usually associated with various systemic prothrombotic states or specific hepatic conditions, such as cirrhosis or hepatocarcinoma, but also with other malignancies. In this case, the first CT scan promptly excluded solid tumors but showed a chronic liver disorder of unknown etiology. Clinicians thus focused their attention on the chronic hepatopathy *per se*. On admission, an extensive serology screening for *Hepatitis A Virus, Hepatitis B Virus, Hepatitis C Virus, Cytomegalovirus,* and *Epstein Barr Virus* (HAV, HBV, HCV, CMV, and EBV) was performed to rule out possible viral etiology, and microbial cultures and paracentesis were also withdrawn. The gastroscopy showed esophageal varices with no signs of

active bleeding, and band ligation of varices was therefore scheduled on elective regimen of treatment. Serology was negative for viral hepatitis, and hepatic biopsy only showed an inflammatory, but not cirrhotic, hepatopathy. Hematologic laboratory tests and genetic screening (mentioned above) were diriment for diagnosis. In fact, the genetic screening revealed JAK2 V617F mutation and so the patient was diagnosed with a myeloproliferative disease. However, septic shock, recurrent surgeries, and hepatosplenomegaly condition did not allow the distinction between polycythemia vera, essential thrombocythemia, and myelofibrosis and, consequently, osteomedullar biopsy and bone marrow aspiration were scheduled. On an elective regimen, she underwent an osteomedullar biopsy of the iliac crest that revealed primary myelofibrosis with megakaryocytes activation.

3.3 Differential Diagnosis

On admission to the ED, the patient presented with fever and a specific abdominal symptoms, and signs of prehepatic portal hypertension were not clear. Laboratory tests showed neutrophil leukocytosis, normal platelets count, normal first-line coagulation tests, liver function tests (with the only exception of mild hyperbilirubinemia), and high levels of C-reactive protein. Moreover, porto-spleno-mesenteric venous thrombosis and hepatic cavernomatosis were not clearly evident on the first CT scan, and the first diagnostic hypothesis included hepatitis of viral, metabolic, or autoimmune etiology and occult gynecological malignancy. Coagulopathy and other hematologic disorders were not considered at the beginning. Thrombophilic screening was carried out only after ICU admission and showed decreased levels of C and S proteins, LAC 1.65 (mild positive), ANA (anti-nuclear antibodies) 1:160, ACA (anti-centromere antibodies) IgM positive, slightly increased FVIII and absent FVIII inhibitor, and positive JAK2.

3.4 Treatment

The management of this patient has been quite challenging under different points of view. First, the antibiotic therapy required particular attention and remodulation because we faced multiresistant germs. When she was first admitted to hospital care, she was put on piperacillin/tazobactam (4.5 g every 6 h) on an empirical basis but, progressively, her conditions got worse and so piperacillin/tazobactam was switched to meropenem (2 g every 8 h). Subsequently, she was affected by a severe septic shock managed with the adoption of vancomycin (1 g bolus and 2 g/24 h continuously infused), meropenem, and caspofungin (70 mg bolus and 50 mg daily) which in turn have been modified with the addition of tedizolid (200 mg/day) and tigecycline (100 mg bolus and then 50 mg twice a day), while vancomycin was discontinued (see above for other details).

Also, the surgical management was not easy because she first underwent emergency laparotomy with drainage of six liters of peritoneal fluid, bowel manipulation with lysis of adherences and section of a necrotic, perforated, intestinal loop, and because of the severe inflammation and massive bleeding, abdomen was left open in

anticipation of a follow-up procedure. She therefore underwent two abdominal cavity revisions in the next 24 h for bleeding control, and the abdominal wall was closed with a temporary abdominal dressing that works with negative pressure allowing edema reduction, fast re-entry, and protection of abdominal content. Moreover, revisions were scheduled every 48 h until the improvement of patient conditions made the definitive closure safe. A savage treatment, called Meso-Rex bypass, was not possible because mesenteric vein was thrombosed as well.

A crucial aspect in the management of PVT was anticoagulation. She was first started on enoxaparin 4000UI twice a day when PVT was diagnosed. Afterward, in ICU, we put her on continuous infusion of unfractioned heparin (UFH) with aPTT target of 1.5 times greater than normal. When septic shock was solved, UFH was discontinued, and enoxaparin was started again. The efficacy of anticoagulation in patients with evidence of acute PVT has been reported in literature and may result in recanalization of thrombi but, unfortunately, we have not seen it in our patient. Thrombolytic therapy, despite its effectiveness, was not considered in this patient because it was too hazardous [2]. She also received numerous blood transfusions (including erythrocytes, platelets, and plasma) but her laboratory tests showed a picture of pancytopenia even at the discharge from the Gastroenterology department.

3.5 Evolution, Outcome, and Follow-up

The patient's condition gradually improved in ICU, so she was discharged from the ICU after two weeks and admitted to the Gastroenterology Department. Despite the resolution of the shock, she remained septic and on antibiotics and her general condition was mediocre (she lost more than 20 kg of weight and was not able to take care of herself). A new abdomen CT scan confirmed SVT without recanalization. She also underwent a medullary needle aspiration that revealed an increased count of plasma cells and an osteomedullar biopsy of the iliac crest that revealed primary myelofibrosis with megakaryocytes activation. She was definitively discharged after two months of hospital stay and she is now on a follow-up program with hepatologists and hematologists, but therapeutic strategies have not been defined yet.

3.6 Discussion

PVT in healthy young patients usually could represent the first manifestation of a myeloproliferative disorder in about 22–48% of patients; an overt MPD might be diagnosed subsequently in 51% of patients [1]. Its onset may be both acute and chronic, with different clinical presentations. When not adequately recognized and treated, SVT can lead to portal hypertension with subsequent occult bleeding and hypersplenism with pancytopenia that make myeloproliferative disease difficult to diagnose. In our patient, thrombosis also involved splenic and superior mesenteric veins that have been considered only at a later time, and this may have led, as a consequence, to intestinal ischemia and worsening of septic condition [3, 4].

This case is relevant to clinical practice because it highlights how important it is to not focus our attention on one specific problem (even when the diagnosis seems

clear) because this may lead to anchoring bias errors. In fact, at the beginning, the SVT was misdiagnosed, and its relevance was underestimated because our colleagues focused their attention on gynecological malignancy and chronic liver disease of suspected viral etiology, and this has led to a delay in the diagnosis of the prothrombotic condition which in turn has determined a rapid progression toward extremely critical conditions on ICU admission. In fact, despite a negative comprehensive workup, in young patients with atypical abdominal thrombosis without risk factors for hepatopathies, there should be a high suspicion of prothrombotic and myeloproliferative disorders that must be included in the differential diagnostic algorithm of PVT/SVT [1]. SVT in the absence of cirrhosis and hepatocarcinoma is a finding that, despite being uncommon, should be considered because it is easy to diagnose and needs prompt treatment with anticoagulant and/or thrombolytic therapy [2, 4]. Early diagnosis is the only way to prevent late complications of SVT (esophageal varices bleeding and intestinal ischemia) that could be life threatening.

Take-Home Messages

- Despite being rare, portal vein thrombosis can be the first presentation of a myeloproliferative disease.
- A high degree of suspicion is required for a prompt diagnosis of splanchnic vein thrombosis and acute mesenteric ischemia due to the nonspecific symptoms of these conditions.
- Due to improvements in imaging, the diagnosis of both acute mesenteric ischemia and splanchnic venous thrombosis has become timelier and more accurate.
- Early diagnosis and anticoagulant management are essential to stop thrombus extension and obtain recanalization.
- Consequences of misdiagnosed portal and mesenteric vein thrombosis may be life threatening leading to bowel perforation and sepsis with septic shock.
- In patients with unclear clinical presentation, it is important to be aware of anchoring bias to avoid missing rare diagnoses.

Summary

Portal vein thrombosis (PVT) is a condition characterized by narrowing or occlusion of portal vein that is usually seen in patients with hepatic cirrhosis or malignancies, but presentation in otherwise healthy young patients is rare. We report a case of a 42-year-old lady, whose medical history was unremarkable, who has recently sought medical attention for fever, ascites, abdominal pain, and hepatosplenomegaly associated with high levels of CA-125. Few days prior hospitalization, she had taken a computed tomography that did not show clear signs of PVT. A standard comprehensive workup did not show any overt hepatic disease or malignancy but, despite these initial results, other causal factors were not investigated, and CT scan was not repeated on hospital admission. The diagnosis of splanchnic vein thrombosis sustained by a procoagulant disorder was made only after admission to ICU for an extremely severe septic shock caused by bowel perforation. This case shows how aspecific and misleading clinical presentation of a relatively uncommon disorder has determined delay in the diagnosis

and therefore has led to an extremely severe septic shock sustained by multiresistant germs. Moreover, this case highlights the intersection of several of the most important aspects of mesenteric ischemia of venous origin, including the high index of suspicion required to diagnose the patient before progression to transmural necrosis, improved early diagnosis with contrast-enhanced CT, and both the surgical and medical treatment of this condition.

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Necrotizing Fasciitis

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Contents

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Learning Objectives

- Maintain a high level of suspicion of complicated soft tissue infection.
- Early initiation of empirical broad-spectrum antibiotic therapy.
- Request urgent surgical consultation, ideally by the Traumatology Team.
- Perform an urgent imaging test, ideally a soft tissue CT scan.

4

4.1 Introduction

Necrotizing soft-tissue infections (NSTIs) are infrequent but associated with a high mortality grade. An accurate diagnosis is difficult in the early stages, and a high level of suspicion is required. The pillar of the treatment is early surgical debridement backed up by empirical broad-spectrum antibiotic therapy. Management in an Intensive Care Unit is recommended because of the high risk of organ failure as well as physiologic support with aggressive fluid resuscitation, nutritional support, and septic shock management.

Necrotizing infections can be divided into three groups according to the affected area: cellulitis (skin and subcutaneous fat); fasciitis (involvement of the superficial fascia with or without the involvement of the deep fascia – being the most frequently diagnosed), and myosotis with injury at the muscular level. They can also be classified according to the bacteria causing the disease. The three entities can have a monomicrobial or polymicrobial cause, with *Streptococcus pyogenes* being the most frequent bacteria isolated in the case of monomicrobial involvement. Another way of characterizing necrotizing infections is by the presence or absence of an entry point.

Regardless of the affectation level (cellulitis, fasciitis or myositis, or all), the appearance of necrotizing tissue is due to the presence of microthrombi at the capillary level induced by bacterial exotoxins and by the surrounding inflammation, giving rise to the appearance of skin bullae and necrotic ulcers.

Case Presentation

A 45-year-old male came to the Emergency Department due to general malaise along with pain, inflammation, and functional impotence of the right leg secondary to a deep wound at the sole of the right foot, with approximately three months of evolution (Fig. 4.1). No personal disease history was found. Vital signs: Blood pressure 100/50 mmHg, heart rate 103 bpm, respiratory rate 20 bpm, oxygen saturation 100%, and temperature of 38.5 °C.

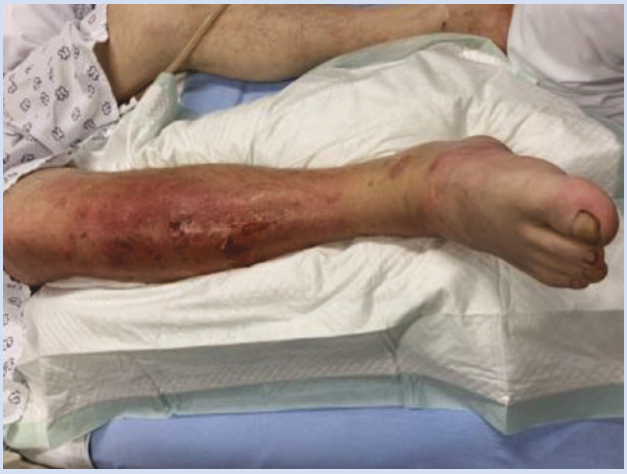

Fig. 4.1 Right foot with clinical signs of soft tissue infection

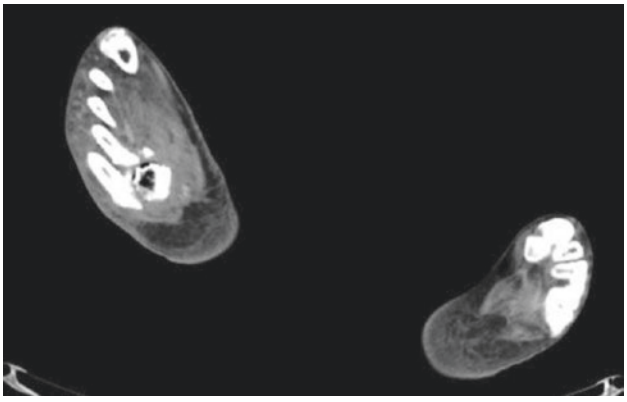

Fig. 4.2 CT scan of the lower limbs with the presence of a right foot ulcer of approximately 3 cm deep with intraosseous gas

4.2 Investigations

We performed the following tests: blood count and coagulation within normal range, lactic acid 6.7 mmol/L, pH 7.28, bicarbonate 18 mmol/L, creatinine 1.26 mg/dL, creatinine phosphokinase 192 UI/L, Na 123 mEq/L, K 5.3 mEq/L, C-reactive protein 386 mg/L, and procalcitonin 7.07 ng/mL. CT scan: right foot ulcer of approximately 3 cm deep with the presence of intraosseous gas, abundant gas in the superficial and deep layers is compatible with necrotizing fasciitis, presence of gas from the foot to the gluteus (Fig. 4.2). Microbiological cultures: soft tissue culture positive for *Streptococcus agalactiae, Streptococcus oralis, Proteus Houseri, Peptostreptocus Anaerobius,* and *Prevotella bivia* with blood cultures negatives (Table 4.1).

Table 4.1 Results of antibiogram culture sample of soft tissue

Antibiotics	(1)	(2)	(3)	(4)
Ampicillin	Sensitive			
Gentamycin				
Erythromycin	Sensitive			
Tetracyline				
Moxifloxacin				
Clindamycin	Sensitive			
Rifampicin				

Streptococcus agalactiae (Group B) (1)
Proteus hauseri (2)
Peptostreptococcus anaerobius (3)
Streptococcus oralis (4)

4.3 Differential Diagnosis

First, a differential diagnosis should be made among necrotizing cellulitis, necrotizing fasciitis, and necrotizing myositis. This can be difficult only with a clinical approach and the diagnosis often is set in the operating room.

Other diagnoses should be considered like gas gangrene or toxic shock syndrome.

4.4 Treatment

Our treatment was based on three major blocks. First, we initiated physiologic support with intensive intravenous fluid therapy, noradrenalin to maintain a MAP around 65 mmHg with the amendment that high blood pressure could worsen the peripheral ischemia, and shock corticoid therapy due to the high dose of vasopressor. Simultaneously, we started the empiric antibiotic therapy with Peperacilin-Tazobactam and Clindamycin. Third, we immediately asked for our Traumatology Team's assessment due to a clear indication of urgent surgical treatment backup by a high Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score. As soon as the patient was hemodynamic and respiratory stable, he was transferred to the operating room where a right supracondylar amputation was made (Figs. 4.3, 4.4, 4.5, and 4.6).

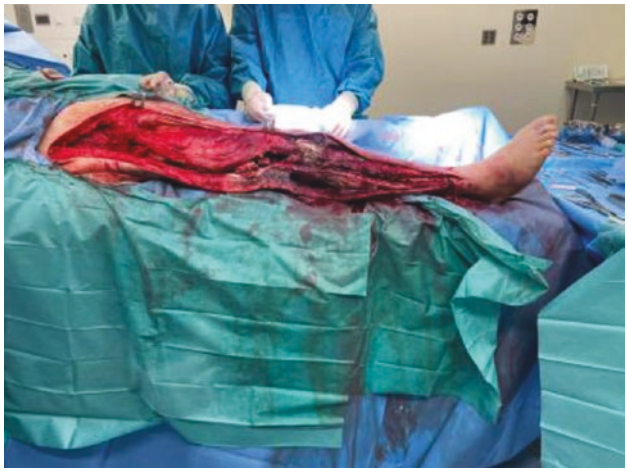

Fig. 4.3 Lateral view of the right foot with the presence of necrotizing tissue

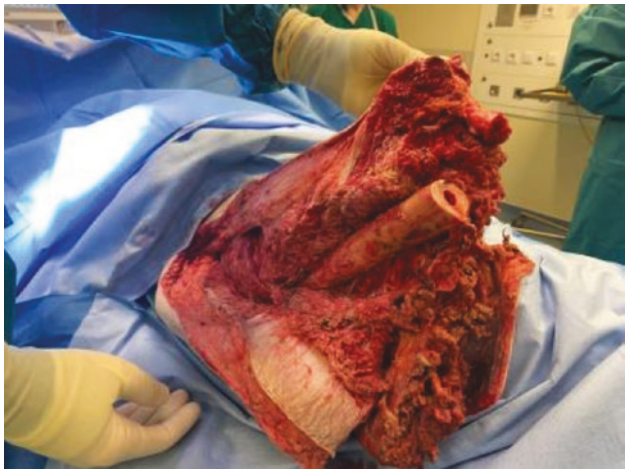

Fig. 4.4 View after urgent supracondylar amputation

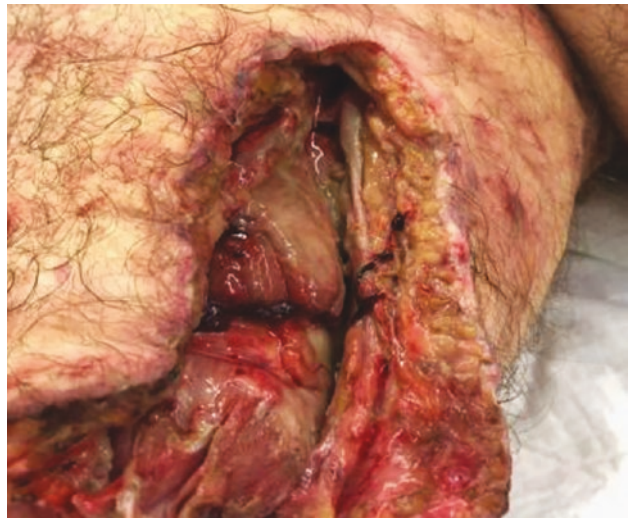

Fig. 4.5 Surgical reexamination of the injury due to persistent fever. Surgical debridement was performed

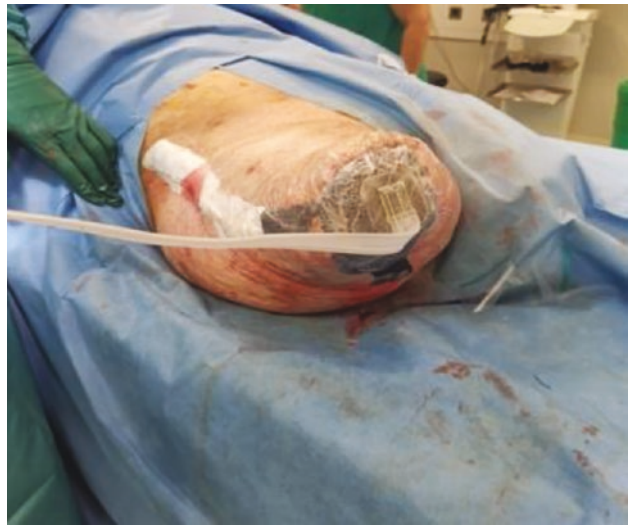

Fig. 4.6 Vacuum-Assisted Closure (VAC) therapy was applied to help the healing process

4.5 Evolution, Outcome, and Follow-up

Despite the broad-spectrum antibiotic that was changed to Meropenem, Vancomicyn, and Clindamycin, the main problem was a prolonged high fever with negative blood cultures and eventually negative tissue cultures. After 44 days of ICU admission, the patient was transferred to a standard care hospital room and eventually was discharged with a modern prosthesis.

4.6 Discussion

Necrotizing fasciitis (NF) is a part of necrotizing soft tissue infections (NSTIs) with a low incidence, but potentially life-threatening and with a high disabling risk. The beginning of the disease can be misleading, and a high grade of suspicion is necessary to establish the diagnosis of NF and appropriate treatment, often in the Intensive Care Unit (ICU) due to the need to prioritize time intervention, especially in patients with septic shock. Necrotizing infections can be divided into three groups according to the affected area: cellulitis (skin and subcutaneous fat); fasciitis (involvement of the superficial fascia with or without the involvement of the deep fascia – being the most frequently diagnosed); and myosotis with injury at the muscular level. It can also be classified according to the bacteria causing the disease. The three entities can have a monomicrobial or polymicrobial cause, with *S. pyogenes* being the most frequent bacteria isolated in the case of monomicrobial involvement.

Laboratory findings are most often nonspecific and can and must be used to assess the gravity of organ dysfunction. The LRINEC score can be helpful to establish a prognosis and help with the decision of surgical intervention, but a low (<6) LRENEC score does not rule out the diagnosis of NF. Blood cultures are positive in approximately half of the patients, especially if necrotizing myositis is present. A radiographic exam with a CT scan is most often necessary to determine the extension of the injury but should not delay surgical intervention when crepitus or rapid progression is present.

Empirical broad-spectrum antibiotic therapy is needed. The most common antibiotic strategy is the combination between Piperacilin-Tazobactam or Meropenem with Vancomicyn or Linezolid and Clindamycin for its antitoxin effects on *Streptococci* and *Staphylococci*. Hemodynamic instability is not rare and may require aggressive fluid therapy and vasopressors like noradrenaline. Capillary leak syndrome associated with streptococcal toxic shock syndrome may appear in which the intravenous immune globulin treatment can be considered. Nevertheless, the medical treatment has to be initiated as fast as possible so that surgical intervention can be performed for being the cornerstone of the treatment. Other treatments like hyperbaric oxygen therapy (HBOT) are not recommended in the latest guidelines because of the lack of evidence and the risk of delaying resuscitation and surgical debridement.

Necrotizing fasciitis as well as other NSTIs remains a diagnostic and therapeutic challenge. A multidisciplinary approach is needed as early treatment can reduce mortality.

Take-Home Messages

- Necrotizing fasciitis is a morbid entity with rapid evolution, high aggressiveness, and a poor prognosis.
- No investigation test can adequately replace diagnosis by surgical inspection.
- An aggressive surgical approach with multiple debridements to healthy tissue is the cornerstone.
- Empirical broad-spectrum antibiotic therapy with double coverage for *Streptococcus pyogenes*, methicillin-resistant *Staphylococcus aureus*, and anaerobic germs.
- Multidisciplinary management in the Intensive Care Unit.

Fournier's Gangrene Secondary to Perforated Retrocaecal Appendicitis: A Turbulent and Prolonged ICU Admission

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Contents

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Learning Objectives

- Understanding the manifestation and early signs of Fournier's gangrene.
- Becoming familiar with the investigation and management of Fournier's gangrene.
- Understanding the intricate involvement of the multi-disciplinary team in complex cases in Intensive Care.

5.1 Introduction

Fournier's gangrene is an acute necrotic infection of the genital, perianal, or perineal region. It is a severe, rapidly evolving, and life-threatening disease with high mortality rates reported between 20% and 88% across multiple case series [1]. It can be monomicrobial, but is often polymicrobial, with enteric gram-negative bacteria predominating. Predisposing factors include diabetes, old age, excess alcohol intake, poor nutritional state, and other causes of immunocompromise. Early recognition and resuscitation, aggressive surgical debridement, and broad-spectrum antibiotic cover are required to manage the condition. Severe cases often require admission to Intensive Care.

It most often arises from anorectal and urological pathologies but can occasionally present secondary to an intra-abdominal infection. Here we present an interesting case of a 52-year-old male with an atypical presentation of Fournier's gangrene secondary to a delayed presentation of a perforated retrocaecal appendix. We share key factors which aided his long and protracted recovery in ICU and explore ways in which to prevent such cases from happening again.

Case Presentation

A 52-year-old male with a past medical history of asthma had presented to the Emergency Department of a local district general hospital (DGH) 6 days prior with a 1-day history of RLQ abdominal pain and diarrhoea. He had no nausea, vomiting, haematochezia, nor urinary symptoms. He reported having eaten out a lot recently but had no recent travel. He was a non-smoker, fit and independent, and he was fully vaccinated for COVID-19.

On examination, there was mild tenderness on palpation of the RLQ. Rovsing's and Murphy's signs were negative, the abdomen was soft, and there was no guarding nor rigidity. He appeared clinically dehydrated. He had a mild pyrexia of 37.9 °C, and the rest of his observations were normal. Bloods showed a normal white cell count (WCC) of 9.69 × 10^9/L but neutrophilia of 8.47 × 10^9/L, a raised CRP of 146 mg/L, and an eGFR of 58 mL/min/1.73 m^2. A venous blood gas (VBG) showed pH 7.38, pCO_2 5.83 kPa, base excess +1, HCO_3 22.8 mmol/L, and lactate 1.6 mmol/L. A urine dipstick was normal except for 2+ protein and 1+ ketones. No stool samples were taken.

Differential diagnoses would have included gastroenteritis, appendicitis, and diverticulitis. He was treated for gastroenteritis with dehydration and was reported to have improved significantly with IV fluids and analgesia. His case was discussed with a consultant, he was given

advice on adequate analgesia, hydration, safety-netted for red flag signs (although unspecified), and was discharged that day.

Six days later, he re-presented and was immediately transferred to the local surgical unit in Oxford, with persistent RLQ abdominal pain, intermittent fevers with rigors, a distended abdomen, reduced appetite, and dysuria. On examination, he had a peritonitic abdomen.

5.2 Investigations

Bloods showed a raised WCC of 16.64 × 10^9/L, neutrophilia of 14.83 × 10^9/L, stage 2 AKI (creatinine 257 μmol/L), CRP of 469 mg/L, and a VBG showed pH 7.35, pCO_2 4.31 kPa, base excess −6.3, HCO_3 18.3 mmol/L, and lactate 3.4 mmol/L.

A CT abdomen-pelvis showed (1) complicated perforated appendicitis with a 75 mm gas-containing focal fluid collection in the right paracolic gutter, (2) small bowel obstruction (likely secondary to adhesions), and 3) non-specific subcutaneous soft tissue fat stranding and oedema in the suprapubic region extending into the scrotum, associated with a right hydrocoele (Fig. 5.1).

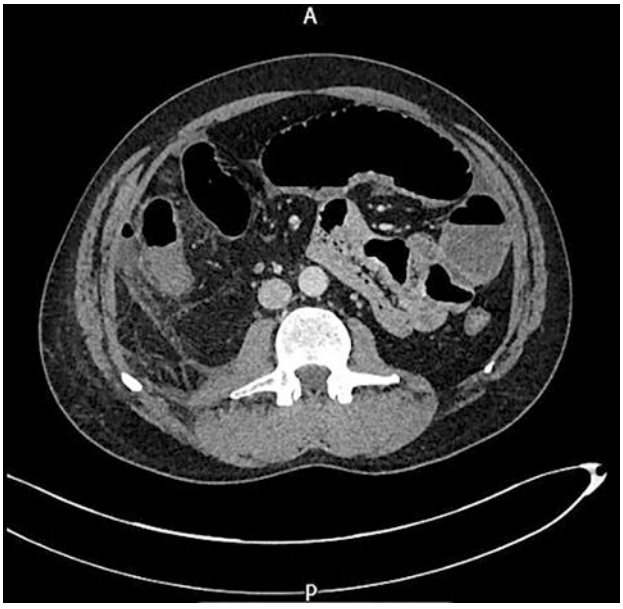

Fig. 5.1 Initial CT abdomen and pelvis showing acute appendicitis complicated by perforation and a 75 mm gas-containing focal fluid collection in the right paracolic gutter and small-bowel obstruction

5.3 Differential Diagnosis

Differential diagnoses at the point before imaging would have included:
1. Perforated appendicitis
2. Perforated diverticulitis
3. Pyelonephritis

5.4 Treatment

On initial presentation he was given IV fluids, co-amoxiclav, and a dose of gentamicin. After the CT was reported, the patient was taken to theatre by the general surgeons for a laparoscopic appendicectomy. The procedure was converted to a laparotomy due to findings of multiple intra-abdominal abscesses, thick adhesions around the right colon, and a serosal tear in the small bowel due to massive distension. An enterostomy was performed through the serosal tear, all abscesses were destroyed, the gangrenous appendix was dissected from the colonic wall and found to have a healthy base, and a full 4-quadrant washout was performed. The appendix histology was later found to be benign. Culture from the pus showed mixed faecal flora. The patient was electively transferred to the ICU for inotropic support and close monitoring after the operation and was intubated and ventilated.

Following extubation on day 2 of ICU admission, it was noticed that he had a red, swollen, tender scrotum, and lower abdominal pain on palpation. He was afebrile and his WCC and CRP were down-trending, with a lactate of 1.5 mmol/L. There was a concern about a potential collection or abscess post-surgery, and of Fournier's gangrene secondary to an infection tracking down from the abdomen.

A CT abdomen-pelvis was performed, which was reported as: 'inflammatory changes of the scrotal content, presumed reactive. Enhancing hydroceles in the scrotum may be infected.' A junior general surgical trainee was contacted and felt it was more likely an abdominal wall cellulitis, and the urology registrar felt it was less likely to be Fournier's as the area was not particularly painful, there was no palpable crepitus nor signs of necrosis, and bloods were improving. On the following day, an ultrasound of the testes was performed as advised by radiology which showed bilateral complex loculated scrotal collections and bilateral epididymo-orchitis, and a repeat CT the same day showed subcutaneous fat stranding in the anterior lower abdomen.

He was taken back to theatre for scrotal debridement by the urologists in view of findings potentially in keeping with early Fournier's gangrene. They found pus and necrotic tissue throughout the scrotum. The right testicle was black and not viable, but the left testicle was intact. The right hemiscrotum was washed out and dead tissue debrided, including the right testicle and scrotal skin. On day 6, the patient went back to theatre for a second-look debridement. Necrotic fat was visualised coming down alongside the right cord stump with pus tracking alongside, which was debrided. On day 8, there was worsening tracking of suprapubic and right inguinal

skin erythema—he was taken back to theatre in a joint procedure with urology and general surgery. Pus was found in the anterior upper right thigh and thus evacuated necrotic tissue at the base of the penis was excised, and the left inguinal region was incised to communicate behind the mons to allow drainage (Fig. 5.2). The following day, he underwent further debridement with a joint look by plastics and general surgery. The operation revealed that there was no significant progression in erythema or necrosis, and no further re-look surgeries were required.

Complex wound care in ICU was essential to his recovery. On return from theatre, he had open wounds in the lower abdominal and inguinal region which were left open until his nutritional status improved to promote the wound healing process, but the wounds were complicated by an ESBL infection. The tissue viability team implemented VAC therapy to facilitate the removal of thick exudates and infectious material. Many studies have demonstrated that negative pressure wound therapy promotes fibrinogenesis, angiogenesis and the activity of leukocytes and macrophages. Prontosan solution was used to circulate through the dressing and irrigate the wounds due to its antimicrobial and antiviral properties. A flexiseal was put in place with laxatives required to maintain liquid stools, in order to minimise wound contamination. Clean granulation tissue was present after 4 weeks of treatment with VAC therapy (Fig. 5.3). On day 41 of admission, he finally returned to theatres for closure of his abdominal wounds (Fig. 5.4) and a split-skin graft of abdominal and perineal wounds.

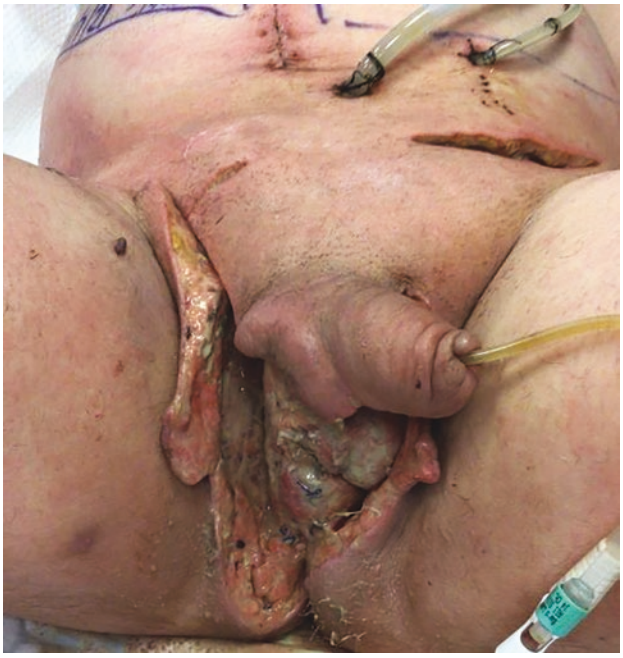

Fig. 5.2 Early stages of the wound prior to application of VAC therapy

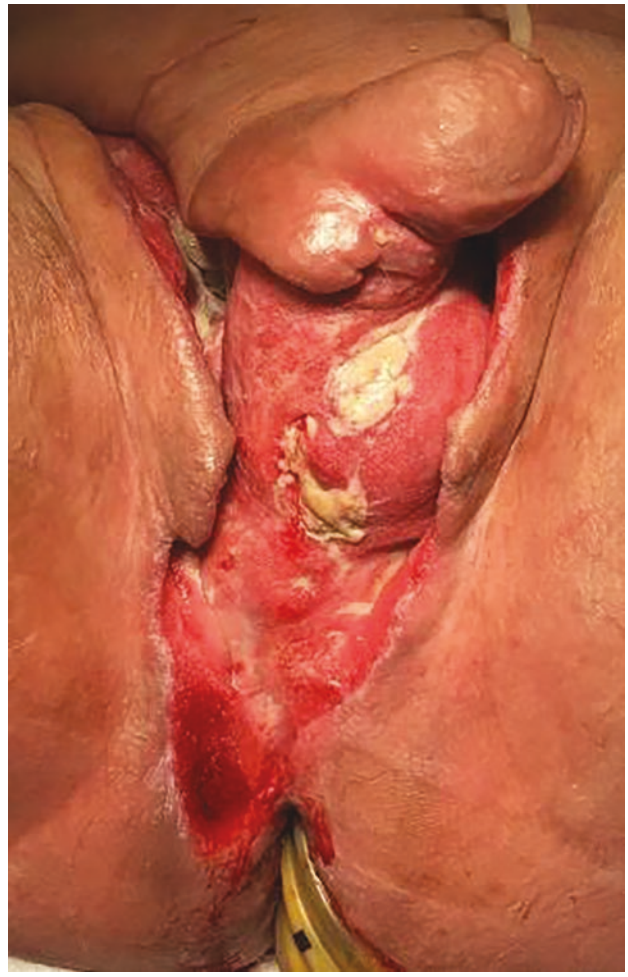

Fig. 5.3 Late stages of wound healing prior to surgical closure

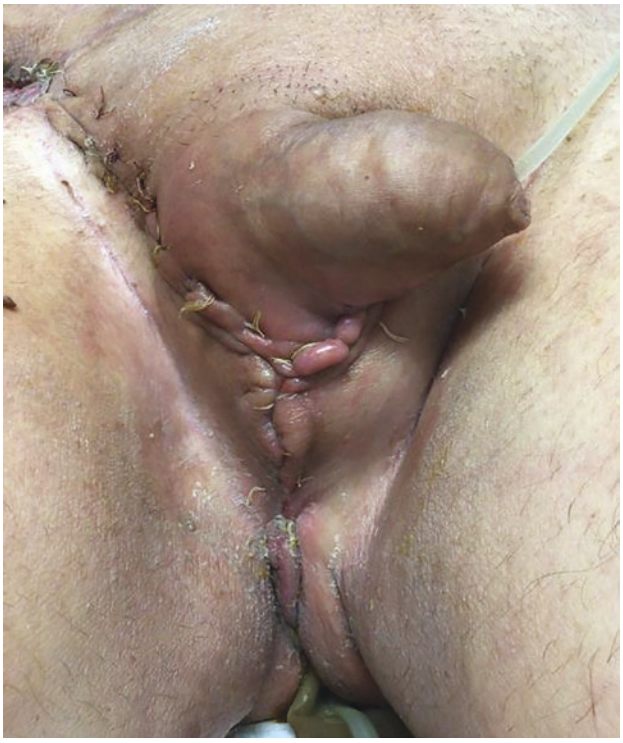

Fig. 5.4 Sutured wound post-surgical closure

5.5 Evolution, Outcome, and Follow-up

His course on ICU was a turbulent one. His APACHE2 score on admission was 18 points, giving him a significant 12% estimated chance of postoperative mortality. Neurologically, the choice of sedatives and his sedation wean strategy were a huge challenge given the increased metabolic demands due to sepsis and prolonged mechanical ventilation. He was paralysed with atracurium for 23 days and sedated with propofol for 54 days, fentanyl for 49 days, and midazolam for 53 days. Patient-controlled analgesia in the form of fentanyl and oxycodone was also used. During his weaning strategy, he was started on regular olanzapine and PRN lorazepam to help his wean and to reduce agitation. The challenge arose from prolonged mechanical ventilation, sedation and paralysis, generalised weakness, agitation, delirium, and secretion load. His prolonged ventilation raised dilemmas when it came to extubation including whether he would benefit from an early vs. late tracheostomy, or to completely avoid a tracheostomy wean. The rationale behind these challenging questions was to increase the number of ventilator-free days and reduce the likelihood of ventilator-associated pneumonia, tracheomalacia, and overall mortality. However, after consulting the literature, there was no clear evidence found for a link between the timing of a tracheostomy wean and any decrease in mortality or increase in ventilator free days [2]. He was thus extubated without a tracheostomy wean.

From a cardiovascular perspective, he developed multiple episodes of arrhythmia in the form of brady-arrythmias, peri-arrest rhythms, and cardiac arrest. These episodes were spontaneous and self-terminating and therefore agents like clonidine were stopped to avoid their recurrence. He was referred to the Cardiology Electrophysiology team who inserted a tunnelled VVI pacemaker with a backup rate of 50 beats/min to avoid any further asystolic events. Unfortunately, he developed multiple subsegmental pulmonary emboli and multiple central line thromboses which were treated with therapeutic anticoagulation (dalteparin). His anticoagulation therapy had to be modified to intermediate weight-based anticoagulation due to a subsequent upper gastrointestinal bleed (melaena), which was investigated by the Gastroenterology team. An upper GI endoscopy was performed which revealed oesophageal and gastric erosions, and he was started on high-dose proton pump inhibitors. Other issues included acute kidney injury (requiring continuous veno-venous haemodialysis) and sepsis (secondary to both ventilator-associated pneumonias and line sepsis which required multiple courses of antibiotics due to the presence of antibiotic-resistant pseudomonas).

All in all, the multi-disciplinary approach by nurses, physiotherapists, and intensive care physicians helped to wean him from the ventilator and extubate him on day 55. On day 59, he was discharged from ICU to the ward. On the ward, he progressed well with physiotherapy, and he was eventually discharged from hospital on day 74. He is now recovering well at home with his partner.

5.6 Discussion

The rare, life-threatening complication of a common disease provides many learning points to improve its outcomes. In developed countries, acute appendicitis occurs at a rate of 5.7–50 patients per 100,000 inhabitants per year, with a peak between the ages of 10 and 30 years [3]. A study has shown that rates of perforated appendicitis are seen more between 0–9 years and after 50 years of age [4], possibly secondary to late diagnoses with other differentials becoming more common in the older population. How do we prevent delay of the initial diagnosis in future cases like this one? Use of diagnostic scores in acute appendicitis were not documented in the clerking of the initial presentation here but can be used to guide further management. A retrospective Alvarado score and RIPASA score in this case show a possible and likely appendicitis respectively, which may have triggered the clinician to escalate the case further by organising imaging.

Fournier's gangrene is a rare but known complication of intra-abdominal infections—roughly 1.6 cases per 100,000 population [5]. The caecum and retroperitoneal appendix lie in the anterior pararenal space, which is in communication with extraperitoneal pararectal and para-vesical spaces of the pelvis, enabling the spread of infection. This case is unique in that the patient had no significant risk factors to develop Fournier's gangrene (e.g. immunocompromise, diabetes, and old age) nor significant anatomical variants (e.g. Amyand's hernia). However, the retroperitoneal position of his appendix may have led to a delay in diagnosis. This case illustrates

how critical early multi-disciplinary team intervention is in enabling optimal outcomes, with this patient being taken back to theatre within 24 hours of a clinician noticing his scrotal erythema.

Scoring systems for severity of Fournier's gangrene can also be used to direct management. A retrospective study looked at the link between UFGSI (Uldag Fournier's Gangrene Severity Index) scores [6], comprised of variables such as physiological parameters, dissemination, age, and patient outcome. Patients with UFGSI scores >18 had a high probability of death and should thus have a low threshold for escalation to ICU-based care, whereas patients with scores <9 had a high probability of survival and rarely needed ICU—they may be treated in the ward to avoid unnecessary costs or morbidity to ICU.

Key and unique aspects of management in this case include (1) the rare and preventable near-fatal complication of a common disease, (2) early and aggressive multidisciplinary surgical management requiring a total of 6 operations, (3) complex and delicate wound management by the tissue viability team and nurses, and (4) daily MDT input in making clinical decisions to prevent and treat the plethora of medical and surgical consequences of his critical illness. Ultimately, we as clinicians should act vigilantly to avoid such delays in initial diagnosis that lead to such life-threatening and costly complications.

Take-Home Messages

- Early diagnosis is key. Simple measures, such as using risk-stratifying scores (e.g. Alvarado, RIPASA) when triaging patients presenting with abdominal pain, giving specific and written red flags for patients, and reassuring patients not to worry about re-presenting, could save lives.
- Consider regular scrotal examinations in male patients presenting with complicated intra-abdominal infections, with a high index of suspicion for signs of Fournier's gangrene—persistent pyrexia, genital pain, scrotal swelling and erythema, and local crepitus. If in doubt, act quickly to seek surgical advice from a urologist and/or arrange a testicular ultrasound.
- Advanced therapies and specialist dressings should be utilised more frequently in complex wound management and use of a faecal management system should be considered. Dietitian input is useful in parallel to optimise wound healing.
- Consider the importance of multi-modal sedation and analgesia to control hyperactive delirium.

Summary

A 52-year-old male presenting to the Emergency Department with abdominal pain, and a high CRP was initially sent home with a diagnosis of gastroenteritis. Six days later, he re-presented in septic shock, with persistent right lower quadrant (RLQ) pain, fever, and abdominal distension. A CT abdomen-pelvis showed a perforated retrocaecal appendicitis, and he was electively admitted to the Intensive Care Unit (ICU) after a laparotomy. Two days later, he developed right-sided scrotal erythema, swelling, and

lower abdominal tenderness. He was returned to theatre for scrotal debridement but eventually required six re-look operations amongst the urology, plastics, and general surgery teams due to progression of Fournier's gangrene. The 59-day ICU admission was complicated by sepsis, pulmonary emboli, acute kidney injury, delirium, a prolonged mechanical ventilation wean, and multiple episodes of cardiac arrest. The patient made a prolonged but excellent recovery with crucial multi-disciplinary involvement, with an emphasis on early surgical intervention, complex wound management, and regular physiotherapy.Acknowledgements Our thanks go to this patient for letting us tell his clinical story—we are extremely glad that he is making a good recovery.

5

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The Use of Venous–Venous Extracorporeal Membrane Oxygenation in a Patient with Severe Acute Respiratory Distress Syndrome and Multiple Organ Failure Due to Septic Shock: A Case Report

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Contents

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Learning Objectives

- Management of septic shock
- Continuous renal replacement therapy in septic shock
- Acute respiratory distress syndrome and venous–venous extracorporeal membrane oxygenation

6.1 Introduction

Sepsis affects millions of people every year with high mortality and morbidity, frequently leading to longer hospital and Intensive Care Unit stay and systemic sequelae. The Surviving Sepsis Campaign International Guidelines for the Management of Sepsis and Septic Shock provide guidance on the care of hospitalized adult patients with sepsis. According to the guidelines, the optimal timing for initiating antimicrobial therapy is based on the likelihood of sepsis and presence of shock [1]. The use of empiric coverage with broad spectrum antibiotics and antifungals should be determined by patient clinical status and risk factors. Regarding hemodynamics, balanced crystalloids over normal saline, and norepinephrine as the first-line vasopressor, are recommended. In case of acute respiratory distress syndrome, a lung protective ventilation strategy should be pursued, using rescue strategies in case of moderate to severe disease [2]. However, the use of venous–venous extracorporeal membrane oxygenation is still controversial. A personalized mechanical ventilation strategy might be the key for improving patient outcome. Additionally, the selection of patients who may benefit from extracorporeal membrane oxygenation should be guided by clinical necessity, as well as patient possibility of recovery, family expectations, ethical standards, and odds of survival [3].

The aim of this case report is to describe the management and treatment of a patient who manifested with septic shock, severe acute respiratory distress syndrome, and renal failure focusing and discussing rescue strategies including venous–venous extracorporeal membrane oxygenation [4].

Case Presentation

We present the case of a 36-year-old Caucasian woman (height 155 cm, weight 48 kg, and body mass index 15,48 kg/m^2) who was suffering for three days from fatigue, fever, back pain, and progressive breathing difficulties. She was admitted at the Emergency Department of a peripheral hospital. Upon admission, Glasgow coma scale was 15/15 and first monitored peripheric saturation of oxygen was around 90% and normal hemodynamics. Despite the use of a full-face mask-continuous positive airway pressure her gas exchanges worsened and she needed Intensive Care Unit admission. Therefore, the patient was oro-tracheally intubated and connected to a mechanical ventilator. However, progressive worsening occurred, with severe hemodynamic and respiratory impairment requiring vasopressor therapy with suspect for septic shock. The patient rapidly developed acute respiratory distress syndrome with neither response to the first-line therapy nor to rescue maneuvers and acute kidney injury starting continuous venous–venous hemodialysis. Due to progressive clinical deterioration, she was transferred to our regional hub-referring hospital to give her access to extracorporeal membrane oxygenation.

6.2 Investigations

6.2.1 Blood Exams

The following blood exams were performed: biochemical tests, complete coagulation, blood cell count, and toxicology. The exams showed severe leucopenia, increased level of inflammatory indices, and reduced Quick time. The first arterial blood gas analysis reported a mild acute respiratory acidosis and severe respiratory failure (Table 6.1). The arterial blood gas analysis showed severe respiratory impairment with an arterial partial pressure of oxygen/ fraction of inspired oxygen ratio = 70.

Table 6.1 Gas exchange, analytic parameters, and ventilatory setting over time

	ICU admission (spoke)	ICU admission (hub)	Post extracorporeal membrane oxygenation
Blood gas analysis			
pHa	7.30	7.46	7,36
Arterial partial pressure of oxygen (mmHg)	95	75	90
Arterial partial pressure of carbon dioxide (mmHg)	51.1	61	38
Fraction of inspired oxygen (%)	100	100	50
Bicarbonate (mmol/L)	25.2	23	25
PaO_2/FiO_2 ratio	90	70	180
Lactate (mmol/L)	7.4	8.2	2,5
Blood exams			
Leukocyte ($\times 10^9$/L)	0,40	0,65	13
C-reactive protein (mg/mL)	400	317	76
Procalcitonin (mcg/L)	100,2	97,4	0,95
Platelets ($\times 10^9$/L)	20	33	70
Ventilatory parameters			
Plateau pressure (cmH_2O)	26	24	21
Positive end-expiratory pressure (cmH_2O) Driving pressure (cmH_2O) Tidal volume (mL/kg of PBW)	11 / 6	12 13 4	10 11 4

Legend: *PaO_2* arterial oxygen partial pressure, *FiO_2* oxygen inspired fraction, *PBW* predicted body weight

6.2.2 Instrumental Exams

Chest X-ray, chest computed tomography, and angio-computed tomography were immediately performed. The images showed extensive right-side thickening with pleural effusion. Angio-computed tomography showed peripheral micro-emboli in the branches of both subsegmental pulmonary arteries. Chest X-ray, lung, brain, and total body scan were repeated during Intensive Care Unit stay. Transthoracic echocardiogram showed a nondilated left ventricle with mild left ventricular systolic dysfunction due to diffuse hypokinesia (ejection fraction estimated 40%); preserved right ventricular longitudinal systolic function with hypokinesia.

A first bronchoscopy was performed triggered by the presence of bad gas exchange, showing a hyperemic bronchial mucosa with purulent secretions localized to the right basal pyramid, and microbial samples were collected. During the hospitalization several fiber optic bronchoscopies were performed to ensure the cleaning and the patency of the bronchial lumens and to improve gas exchange. Lung ultrasound exam showed diffuse lung B-lines with extensive right-side thickening with pleural effusion.

6.2.3 Hemodynamic Monitoring

At Intensive Care Unit admission, advanced hemodynamic monitoring was initiated, placing a central venous line, continuous invasive arterial blood pressure, and heart rate monitoring. The urinary output was assessed with a urinary catheter and urinometer hourly. Arterial pressure waveform analysis, cardiac output, continuous central oxygen venous saturation, and central venous pressure monitoring were assessed using a thermodilution system. The body temperature was assessed continuously by an axillary temperature probe and invasively with the thermodilution system.

6.2.4 Microbiology

Blood cultures were positive for methicillin-resistant *S. aureus*. Severe acute respiratory syndrome coronavirus-2 swab tested negative. Throat swabs tested positive for influenza-A H1N1. Legionella and pneumococcus urinary antigens tested negative. Bronchial aspirate sample was positive for methicillin-resistant *Staphylococcus aureus*, *M. catarrhalis*, and H1N1. Bronchoalveolar lavage cultures tested positive for *M. catarrhalis* (10^7 colony forming unit/mL), *S. aureus* (>10^7 colony-forming unit/mL), and varicella zoster virus; pleural fluid cultures tested positive for *S. aureus*; *C. auris* swab was positive. Serologic panel was negative, and varicella zoster virus deoxyribonucleic acid was detected in blood. After twenty days, *Elizabethkingia miricola* was detected in bronchoalveolar lavage fluid.

6.3 Treatment

6.3.1 Emergency Department

The patient arrived at the Emergency Department with a full-face mask under continuous positive airway pressure (fraction of inspired oxygen = 60%, positive end-expiratory pressure = 10 cmH_2O). A broad-spectrum antibiotic therapy with levofloxacin, meropenem, and co-trimoxazole was started. Thoracic computed tomography scan was performed. After respiratory worsening, the patient switched to noninvasive mechanical ventilation (pressure support = 16 cmH_2O, positive end-expiratory pressure = 10 cmH_2O, fraction of inspired oxygen = 70%) but unsuccessful. Gas exchange worsened with arterial partial pressure of oxygen/ fraction of inspired oxygen ratio = 70.

6.3.2 Intensive Care Unit—Peripheral Hospital

Upon sedation and endotracheal intubation, the patient was connected to a mechanical ventilator (pressure control ventilation = 15 cmH_2O, positive end-expiratory pressure = 11 cmH_2O, mandatory respiratory rate = 20 bpm, fraction of inspired oxygen = 100%, and tidal volume = 8 mL/kg of predicted body weight), achieving a lung protective ventilation strategy. Hypercapnic acidosis and severe hypotension resistant to fluid load (30 mL/kg) with crystalloids and norepinephrine up to 0.3 mcg/kg/min appeared. After microbial results, antibiotic therapy was changed, starting ceftaroline and oseltamivir, continuing levofloxacin and meropenem. Due to anuria and increased level of serum lactate, continuous replacement renal therapy was started. Severe leucopenia was treated with human normal immunoglobulin infusion. Given the inability to improve the gas exchange with mechanical ventilation, the patient was positioned prone with minimal improvement (arterial partial pressure of oxygen/ fraction of inspired oxygen = 85) and was transferred to referral hub-center.

6.3.3 Intensive Care Unit—Hub Hospital

6.3.3.1 Respiratory Treatment

The patient was mechanically ventilated in pressure control mode according to a lung protective ventilatory strategy achieving partial improvement. Gas exchange rapidly worsened (arterial partial pressure of oxygen/fraction of inspired oxygen = 50 and arterial partial pressure of carbon dioxide = 61). Despite the pressure/volume tool showed an optimal positive end-expiratory pressure of 17 cmH_2O, hemodynamic instability allowed <12 cmH_2O. Venous–venous extracorporeal membrane oxygenation was started (blood flow rate = 5 L/min on 3500 rpm, fresh gas flow = 2 L/

min, and fraction of inspired oxygen = 60%). Ventilator setting: pressure control = 14 cmH_2O, positive end-expiratory pressure = 12 cmH_2O, respiratory rate = 18 breaths/min, fraction of inspired oxygen = 100%, plateau pressure = 24 cmH_2O, and tidal volume = 4 mL/kg. During 10 days of extracorporeal membrane oxygenation, adequate cardiac output, and oxygen delivery, hemoglobin>8 g/L with multiple blood transfusions, controlled arterial partial pressure of carbon dioxide, minimizing patient's acidosis, oxygen saturation = 85%, with arterial partial pressure of oxygen>55% were guaranteed [4]. We treated fever and reduced inotropes when possible.

6.3.3.2 Hemodynamic

At admission, high dose-inotrope was used (norepinephrine up to 0.7 mcg/kg/min and epinephrine up to 0.2 mcg/kg/min). Cardiac ultrasound showed a reduction of ejection fraction (estimated 35%), and continuous infusion of dobutamine 6 mcg/kg/min was added. Due to severe acrocyanosis, epinephrine, and norepinephrine were stopped, and a fluid load with crystalloids was done. Advanced hemodynamic monitoring showed low vascular resistances and possible permeability lung edema. After one week from the admission, the inotropic support was progressively reduced and stopped.

6.3.3.3 Infectious Disease

Antibiotic therapy with levofloxacin and oseltamivir continued for 14 days, while imipenem was stopped for negative cultures. Daptomycin and linezolid were added. Because of pancytopenia and immunodepression, empiric caspofungin was started considering the high risk of invasive candidemia (candida score > 3). Caspofungin was stopped when serum beta-glucan was negative. Inflammatory indices progressively decreased. On day seven, acyclovir was added for varicella zoster virus in broncho aspirate and blood. On day 37, caspofungin was administered for *Candida auris*, and vancomycin was started for *Clostridium difficile* in feces. On day 47, piperacillin-tazobactam was started for multidrug-resistant pseudomonas in blood. On day 52, cefiderocol was started for *Elizabethkingia miricola* on broncho aspirate. Intravenous hydrocortisone 200 mg/day was initiated the day of Intensive Care Unit admission.

6.3.3.4 Renal Replacement Therapy

The patient arrived in our department with metabolic acidosis, increased level of serum lactic acid, increased inflammatory indices, oligo-anuria, and increased level of creatinine and urea. She underwent continuous venous–venous hemodialysis. When the renal function recovered with spontaneous urine output, continuous renal replacement therapy was discontinued (day 42).

6.3.3.5 Hematology

The patient presented severe pancytopenia (white blood cells = $0.49x10^9$/mcl; neutrophils = $0.48x10^9$/mcl; platelets = $20x10^9$/mcl). She was transfused with blood, plasma, and platelets. Lenograstim was continued to stimulate bone marrow. After 1 week, significant improvement was observed, and 1-month later she started subcutaneous injection of human erythropoietin 10,000 UI.

6.3.3.6 Surgery

The patient presented severe acrocyanosis and the marbling came to the root of the limbs. She developed peripheral micro-emboli with septic gangrene of the four limbs. After the results of upper and lower limbs arteriography, in accordance with clinical findings and Doppler ultrasound, amputation of the four limbs was necessary. No postoperative complications occurred.

6.3.3.7 Nutrition

Minimal enteral feeding was started within the first 12 hours of Intensive Care Unit admission (6 kcal/kg/day), together with parenteral nutrition (22 kcal/kg/day). Enteral nutrition was continued with a target of 30 kcal/kg/day until extubation and rehabilitation, thus proceeding with spontaneous enteral feeding. Glycemia was monitored 3 times/day, and if necessary, insulin was administered following standardized protocols.

6.4 Evolution, Outcome and Follow-up

After extra corporeal membrane oxygenation therapy, she developed pneumonia, pneumothorax, and air leak syndrome. On day 17 tracheostomy was performed, followed by progressive reduction of sedative drugs and pressure supports on the ventilator. Recurrent right pneumothorax, lung computed tomography scan, lower tidal volumes than expected, continuous air leak, and multiple fibro-bronchoscopy were suggestive for bronchopleural fistula. During operative fibro-bronchoscopy, four bronchial blockers were placed to functionally exclude the intermediate lobe, but thoracic surgery was necessary. The inferior pulmonary lobe was removed because completely hepatized (Fig. 6.1a, b). After the four limbs amputation, she had a

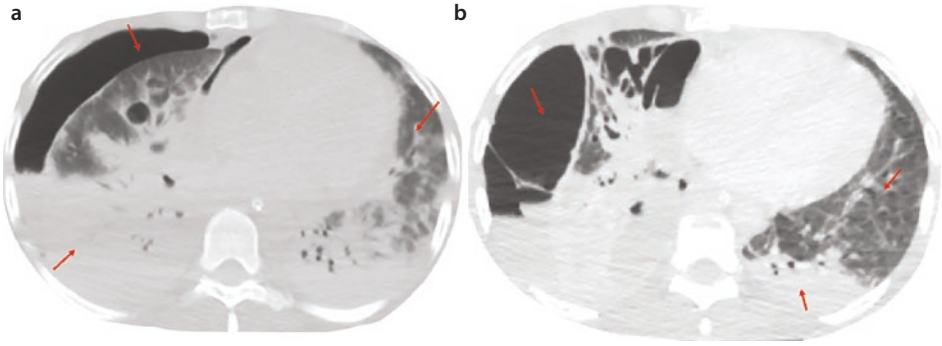

Fig. 6.1 Chest computed tomography before extracorporeal membrane oxygenation and before placing bronchial blockers. Figure legend: Right pneumothorax and consensual atelectasis of the right inferior lobe and bilateral ground-glass infiltrates before extracorporeal membrane oxygenation **a**, and before **b** placing bronchial blockers

complete recovery. She was therefore extubated, she recovered the urinary output with normal kidney function, and antibiotics were stopped. The patient is currently waiting for the latest generation prostheses.

6.5 Discussion

We report a case of a young woman with refractory septic shock, severe acute respiratory distress syndrome, and multiple organ failure who was treated with rescue therapies. The main message of this clinical case is the speed of decision-making associated with the adherence to guidelines. First, once the patient was deemed untreatable with the resources of a spoke center, she was immediately transferred to the hub referring hospital to receive high standard of care. Broad-spectrum antibiotic therapy was targeted to specific pathogens after culture result, the prompt use of crystalloids and inotropes according to the Surviving Sepsis Campaign guidelines improved hemodynamic stability, and the adoption of a lung-protective ventilator strategy with the use of rescue therapies was essential for patient recovery while waiting for the transfer to the hub-hospital. Accordingly, the patient needed to start venous–venous extracorporeal membrane oxygenation, fulfilling the criteria for treatment start (mortality risk >50% and arterial partial pressure of oxygen/fraction of inspired oxygen<150 with fraction of inspired oxygen>90%, hypercapnia and poor gas exchange despite protective ventilation, prone positioning, and recruitment maneuver). During the Intensive Care Unit course, driving pressure was maintained<13cmH_2O, Plateau pressure < 27cmH_2O, and tidal volume between 4 and 6 mL/kg regardless of the disease phase, according to ultra-protective ventilation strategy [3]. The weaning from venous–venous extracorporeal membrane oxygenation was safe because of focusing on the improvement of underlying conditions, improving gas exchange, and accounting for ventilator-induced lung injury [4]. The renal replacement therapy was performed using a filter capable of removing endotoxins, cytokines, and the other inflammatory mediators from the blood. Thanks to the synergic therapy based on the administration of both human normal immunoglobulin and granulocyte-colony stimulating factors a significative improvement of white blood cell count including neutrophiles was achieved.

Despite the full adherence to the guidelines, four limbs amputation, air leak syndrome due to bronchopleural fistula, and healthcare associated infections appeared. These sequelae resulted from multiple factors: septic shock with peripheral microemboli, septic gangrene, and high-prolonged dose of inotrope drugs.

In conclusion, septic shock is a potential life-threatening condition with high potential for systemic complications and multiple organ failure. The prompt recognition of this condition, rapid management, and correct treatment following current guidelines may positively influence patient outcome. However, being septic shock a condition at high risk of multiple organ failure and death, systemic complications are frequent, thus potentially affecting the recovery phase, and lasting long-term disability.

Take-Home Messages

- Take-home message 1 The goal of therapy in septic shock is the identification and treatment of the disease in earliest stage
- Take-home message 2 The ventilator strategy adopted for acute respiratory distress syndrome ventilation may affect patient outcome: use ultraprotective strategy with lower tidal volume (4–6 mL/kg of predicted body weight), keep plateau pressure < 27cmH_2O, and use positive end expiratory pressure to recruit lungs without affecting driving and plateau pressures.
- Take-home message 3 Venous–venous extracorporeal membrane oxygenation is a valid rescue strategy in severe acute respiratory distress syndrome supporting completely pulmonary function to allow adequate oxygenation and gas exchanges, with limited impact on lung function.
- Take-home message 4 Continuous renal replacement therapy with a hemofilter which remove cytokines in septic shock with multiple organ failure may improve hemodynamic status and lactatemia and decrease the level of inflammatory indices.

Summary

Our clinical case wants to highlight how the adherence to the guidelines associated with prompt and rapid identification of the clinical problem may save lives. A critically ill 36-year-old woman with refractory septic shock due to H1N1 influenza and co-infection with methicillin-resistant *S. aureus* and *M. catarrhalis* rapidly developed multiple organ failure, including acute respiratory distress syndrome and renal impairment. Severe respiratory failure required ultraprotective lung ventilation and rescue strategies [5]. Venous–venous extracorporeal membrane oxygenation was adopted supporting completely the pulmonary function and allowing the recovery [4]. Continuous renal replacement therapy with a hemofilter, which allowed cytokines removal led to recovery of renal function, marked reductions in disease severity scores, and decreased levels of procalcitonin, endotoxin. This approach combined with appropriate antimicrobial therapy led to effective treatment. However, several complications occurred, including septic peripheral micro-emboli and gangrene of four limbs requiring amputation, and pneumothorax with air leak syndrome with bronchopleural fistula. Despite the difficult disease course, the patients recovered and were discharged. This case wants to highlight that the selection of patients who may benefit from extracorporeal membrane oxygenation should be guided by the guidelines, clinical necessity, as well as patient possibility of recovery, family expectations, ethical standards, and possibility of survival [3]. Moreover, the adherence to the guidelines for the treatment of sepsis, acute respiratory distress syndrome, and acute kidney injury have led to patient recovery, although without completely preventing long-term disability.

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Viral Infections in the Intensive Care Unit

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Contents

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Learning Objectives

1. Recognize the importance of viral infections in the Intensive Care Unit, particularly HIV, influenza, SARS-CoV-2, and herpesvirus.
2. Describe the epidemiology and microbiological features of the main viral infections that may lead to admission to the Intensive Care Unit.
3. Outline the clinical manifestations of the most relevant viral infections and the potential complications that may warrant admission to the Intensive Care Unit.
4. Understand the diagnostic workup of viral infections requires a combination of clinical suspicion and complementary tests, including nucleic acid tests, serologic tests, or antigen detection, among others.
5. Summarize the major principles guiding the management of viral infections in the Intensive Care Unit, including the use of specific antivirals and supportive care.

7.1 Introduction

Bacterial infections and sepsis represent the main cause of admission to the Intensive Care Unit (ICU) within infectious diseases, although viral infections are becoming increasingly important in critically ill patients. The use of new molecular diagnostic polymerase chain reaction (PCR) assays has led to increased recognition of the role of respiratory viruses as a potential etiology of pneumonia. Recent studies have shown that 7–36% of community-acquired pneumonia cases with a defined microbial etiology can be attributed to respiratory viruses. In particular, the novel coronavirus severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is currently the focus of the global public and science. Further insights into the role of viral pneumonias as well as the outcome relevance of secondary infections are of utmost importance in this context. In this chapter, we will focus on the management and treatment of human immunodeficiency virus (HIV), influenza, SARS-CoV-2, and herpesviruses in critically ill patients.

7.2 Human Immunodeficiency Virus (HIV)

The human immunodeficiency virus (HIV) is a retrovirus of the genus *Lentivirus*, which infects crucial cells of the human immune system, particularly cluster of differentiation (CD)-4$^+$ T helper cells, macrophages, and dendritic cells. HIV causes a wide spectrum of diseases ranging from asymptomatic infection (despite active viral replication) to an acquired immunodeficiency syndrome (AIDS), in which life-threatening opportunistic infections and tumors may develop. Two species of HIV may cause disease in humans: HIV-1 (more virulent, infective and prevalent) and HIV-2 [1, 2].

7.2.1 Epidemiology

The World Health Organization (WHO) estimated a global prevalence of HIV infection of 0.7% in adults in 2021, although the burden of the epidemic varies

markedly between countries and regions. About 60% of people infected with HIV live in sub-Saharan Africa, where the overall prevalence rises to 7%, exceeding 25% in some specific countries (Botswana, Lesotho, Swaziland and South Africa). Although there is a downward trend in new infections in the last years, 1.5 million people were newly infected with HIV in 2021. Since the first description of AIDS in the United States in 1981, the disease has spread rapidly to become the worst pandemic of the twentieth century, causing more than 40 million of deaths, a figure comparable with that of the influenza pandemic at the beginning of the twentieth century. Mortality has fallen dramatically since the introduction of combination antiretroviral therapy (ART), but still 650,000 people died from AIDS-related illnesses in 2021 [3, 4].

7.2.2 Virology

As a member of the *Retroviridae* family, HIV has the ability to integrate its ribonucleic acid (RNA) into the host genome, which makes it extraordinarily difficult to eradicate. From a structural perspective, HIV is composed of two copies of positive-sense single-strand RNA which code for the viral genes and a conical capsid composed of hundreds of copies of the viral protein p24, inside of which there are viral essential elements such as reverse transcriptase, protease, ribonuclease, and integrase. A matrix composed of the viral protein p17 surrounds and protects the capsid. This structure is surrounded by the viral envelope, which is composed of a lipid bilayer taken from the human host cell and the envelope protein (Env) composed by the glycoproteins gp120 and gp41. HIV is transmitted through the contact of infected body fluids with mucosae, blood, or damaged skin. Transmission routes include sexual transmission (i.e., unprotected sex), parenteral transmission (particularly among people who inject drugs, although transmission via blood or blood products is possible), and vertical transmission (i.e. perinatal mother-to-child transmission, during pregnancy, delivery, or breastfeeding). HIV enters the host cell through interaction of the envelope protein and its target on the host cell: CD4, which expressed on the surface of T lymphocytes, monocytes, macrophages, and dendritic cells. To allow the fusion and uncoating of the virus, this interaction requires a co-receptor: C-C chemokine receptor type 5 (CCR5) (R5 virus), C-X-C chemokine receptor type 4 (CXCR4) (X4 virus), or either (R5X4 virus). Then, the viral RNA is reverse transcribed into DNA by reverse transcriptase. Afterward, the viral DNA is imported into the nucleus, where it is integrated into the host genome by viral integrases. HIV takes advantage of host enzymes, which transcribe HIV DNA into viral messenger RNA (mRNA). The mRNA is exported back to the cytoplasm, where translation occurs and viral proteins are produced to generate new mature virions, which are assembled and released. All these steps in the HIV life cycle are potential targets for antiretroviral drugs. HIV-1 exhibits a high rate of variation, which results in one mutation every few replication events. Thus, survival and thrive of each specific variant depend on the host's immune system and antiretroviral medications pressure [1].

Clinical Presentation

HIV infection causes a wide spectrum of disease, from asymptomatic to life threatening, which may be grouped in up to five categories [2]:

1. Acute retroviral syndrome (ARS). ARS is the most common initial presentation in patients infected with HIV, which is associated with high viral RNA levels after the eclipse phase (i.e., the phase immediately after HIV infection, where the virus replicates in the host but no laboratory markers are consistently detectable, which usually lasts 1–3 weeks). It is symptomatic, self-limiting phase (usually <2 weeks) characterized by a mononucleosis-like syndrome (fever, lymphadenopathy, nonspecific rash, sore throat, myalgia/arthralgia, diarrhea, weight loss, headache, and/or malaise), although severe complications may occur (e.g., encephalitis, myocarditis, or multiple organ failure due to hemophagocytic lymphohistiocytosis). The severity of the constellation of symptoms correlates with peak viral load during this phase. Once the immune response develops, viral RNA levels drop dramatically to a steady-state level that is known as the viral set point.
2. Immune processes related to host responses against chronic viral infection in the absence of ART (e.g., lymphadenopathy, thrombocytopenia or HIV-associated dementia) or by persistent inflammation even after initiation of ART (e.g., cardiovascular disease, hypercoagulability or metabolic disorders).
3. Opportunistic diseases due to progressive deterioration of the host's immune response. These include some of the main syndromes related to AIDS, such as *Pneumocystis jirovecii* pneumonia, esophageal candidiasis, cytomegalovirus infection, extrapulmonary tuberculosis, Kaposi's sarcoma or lymphoma, among others.
4. Immune reconstitution inflammatory syndrome (IRIS). IRIS is a common complication occurring after the initiation of ART. It consists of a paradoxical worsening of the symptoms of an opportunistic infection or neoplasia already treated or previously undiagnosed within weeks or months after the initiation of ART, which is associated to the improvement of the immune function. Risk factors for IRIS include a high baseline RNA viral load, a low initial $CD4^+$ cell count, and a rapid recovery of $CD4^+$ cells after initiation of ART.
5. Generalized lipodystrophy syndrome. This syndrome occurs in patients under ART, particularly with protease inhibitors. It is characterized by loss of subcutaneous adipose tissue, with hypertriglyceridemia and insulin resistance. These metabolic derangements are associated with increased mortality due to cardiovascular diseases, liver diseases, acute pancreatitis, renal failure, and sepsis.

7.2.3 Diagnosis and Risk Stratification

Due to the wide constellation of nonspecific clinical symptoms produced by HIV infection, a high degree of suspicion is required for early diagnosis. Otherwise, clinicians can often miss the diagnosis. Current guidelines in Europe and in the United

States of America recommend screening with a fourth-generation antigen/antibody combination immunoassay that detects HIV-1 and HIV-2 antibodies (IgG and IgM) and HIV-1 p24 antigen [5, 6]. No further testing is required for specimens with a negative result on the initial immunoassay, unless a there is a high degree of suspicion of HIV infection, in which case nucleic acid test (NAT), particularly RT-PCR, is able to identify acute HIV infection. Patients with a positive result in the initial screening tests should be tested with an antibody immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies and further tested with a NAT if any doubt arises.

Although not included in the diagnostic algorithm, other relevant tests should be obtained to have a full overview of the HIV infection [6]: CD4 cell count and percentage (useful to predict the risk of HIV-related complications and the need for prophylaxis to prevent opportunistic infections), viral load (as it may affect the selection of ART regimen, and it is useful to assess the response to the treatment), resistance testing, and additional tests to inform ART selection (patients who are positive for the HLA B*5701 haplotype should not receive abacavir due to high risk for hypersensitivity reactions, and patients who are candidates to receive CCR5 antagonists should undergo tropism testing). General blood and urine testing, screening for coinfections (viral hepatitis, tuberculosis, and sexually transmitted diseases), and screening for Human Papilloma Virus (HPV)-related neoplasia are also part of the initial laboratory set of tests.

7.2.4 Treatment and Prognosis

Current guidelines recommend that all patients with acute or early HIV initiate ART as soon as feasible, regardless of CD4 cell count and even if results of resistance testing are not yet available. Five therapeutic classes exist, each targeting a unique step in the life cycle of the virus. The selection of ART regimen is outside the scope of this chapter. After initiation of ART, viral RNA levels should be checked on a regular basis to document and ensure viral suppression [6].

Although there are no specific guidelines for the management of ART in the setting of intensive care, it is commonly accepted that HIV patients who have already initiated ART prior to ICU admission should continue ART if possible, with adjustments in case of concerns related to toxicity, organ failure, interactions, or galenic issues. For patients with HIV infection who are not on ART at ICU admission, a recent narrative review on the management of HIV-infected patients in the ICU proposed the following approach [7]: immediate initiation of ART in patients admitted for severe HIV infection, HIV encephalitis, or progressive multifocal encephalopathy; delayed ART initiation in patients admitted for central nervous system (CNS) tuberculosis or cryptococcosis (up to 10 weeks due to the high risk of IRIS in patients with elevated intracranial pressure or delayed clinical improvement); delayed initiation in patients admitted for other opportunistic infections (e.g., *Pneumocystis jirovecii* pneumonia or extra-CNS tuberculosis) (at least 2 weeks); and post-ICU discharge administration in patients admitted for non-HIV-related diseases or CD4 cells >200/μL.

The prognosis of HIV infection has substantially improved thanks to ART. With early initiation of ART and adequate medical care, HIV has become a chronic condi-

tion, which results in a nearly normal life expectancy. Therefore, HIV infection, even at late stages, should never be considered as a stand-alone reason to deny admission to the ICU [7].

7.2.5 Importance in Intensive Care Medicine

Patients with HIV infection are at high risk of AIDS-defining opportunistic infections that may require ICU admission, particularly in cases of unknown infection or limited access to ART. *Pneumocystis jirovecii* pneumonia, tuberculosis, and cerebral toxoplasmosis are the most common of these opportunistic infections in the ICU. However, the leading causes of admission in HIV-infected patients are bacterial sepsis and exacerbation of chronic comorbidities [7]. While ART should be continued in HIV-infected patients who were on therapy prior to ICU admission, an individualized approach to initiation should be used in ART-naive patients in the setting of an ICU admission. When ethical issues arise, it is important to note that in-hospital mortality does not depend on HIV infection characteristics, but rather on age, chronic comorbidities, and extent of organ dysfunction [7].

7.3 Influenza

Influenza is an acute febrile disease caused by a group of viruses from the *Orthomyxoviridae* family, which infect the epithelial cells of the respiratory system. Influenza tends to present as a seasonal disease, causing outbreaks almost every winter and, occasionally, turning into pandemics. Although most patients experience an uncomplicated illness, life-threatening complications may arise. Three relevant genera of influenza virus may infect humans: Influenza A (most virulent, and able to infect other species apart from humans, which leads to more variability and potential to produce pandemics), Influenza B (less virulent, less genetically diverse, and almost exclusively a human pathogen, which prevents the possibility to produce pandemics), and Influenza C (which is the less common and severe) [8, 9].

7.3.1 Epidemiology

The WHO estimates that annual epidemics of influenza may result in up to five million cases of severe illness and up to 650,000 deaths [10]. While human influenza viruses are easily transmitted via respiratory route, other routes are possible in other species, which may contribute to the emergence of pandemics. The burden of pandemic influenza depends not only on the virulence of the circulating strain but also on the level of preexisting immunity. The 1918 influenza pandemic resulted in a high fatality, causing more than 40 million of deaths, a figure comparable with that of the HIV pandemic. Population at risk may benefit from vaccination programs, although their efficacy is suboptimal and is particularly reduced in the case of an antigenic mismatch between the vaccine and the circulating virus [8].

7.3.2 Virology

Influenza viruses are negative-sense, single-stranded, segmented RNA viruses. All the genera of influenza have some common features, including a lipid bilayer envelope, which is obtained from the host cell, and the presence of surface glycoproteins. Among these glycoproteins stand out hemagglutinin (HA), which mediates binding to sialic acid-containing receptors in the host cell and viral entry; neuraminidase (NA), which contributes to the release and spread of the virus; and matrix protein-2 (M2), which allows the release of the viral genome from the virion to the cytoplasm of the host cell (i.e., viral uncoating). The HA and NA glycoproteins exhibit a great antigenic variability, which allows reinfections of the same individual and reduces the effectivity of prevention strategies (vaccines) and treatments. This variability is due to two mechanisms: antigenic shift, which is the ability of the virus to exchange of viral segments (reassortment) with other influenza strains coming from other species, generating new subtypes which may lead to pandemics due to the lack of immunity to that viral subtype; and antigenic drift, which are small antigenic changes in these proteins generated by mutations and selected to improve evasion from the host's immune system. Nomenclature of the virus isolate usually includes the type/genus, host, place of isolation, isolate number, and year of isolation (e.g., A/Turkey/Ontario/6118/1968 (H8N4)), although exceptions are possible (e.g., A/H1N1pdm09 for the virus responsible of the 2009 influenza pandemic). In influenza A viruses, the HA and NA subtype is also commonly described after the viral isolate name [8, 9].

Clinical Presentation

The most common clinical picture in patients with uncomplicated illness consists of abrupt-onset fever, shaking chills, headache, myalgia/arthralgia, and malaise, together with unspecific respiratory symptoms (cough, chest discomfort, sore throat, hoarseness, nasal discharge, etc.). The most common time evolution of the disease includes a 2-day incubation period, followed by a 3-day period of systemic symptoms, after which fever tends to disappear, giving way to a 1 to 2-week period of recovery, where asthenia, malaise, and respiratory symptoms predominate. The clinical presentation may vary in children, where gastrointestinal symptoms and febrile seizures are sometimes present; in older adults or immunocompromised individuals, where the initial symptoms tend to seem milder, but may progress to severe disease; and depending on the type of influenza (e.g., H1N1pdm09 virus was commonly associated with vomiting and diarrhea, H3N2 virus was frequently associated with parotitis, etc.) and on the immune status of the host (vaccinated people tend to present milder symptoms) [8, 9].

Although virtually any patient may experience a complicated illness, some specific populations are at higher risk (children <5 years and adults >65 years of age, pregnant woman, patients who live in nursing homes or long-term care facilities, and people with chronic underlying diseases). The most relevant complications from the perspective of Intensive Care Medicine include:

- Primary viral pneumonia. This is the most common complication of influenza, and should be suspected in patients with non-improving or worsening symptoms after 3–5 days. Acute respiratory failure presents with dyspnea, tachypnea or hypoxia and may evolve to acute respiratory distress syndrome (ARDS).
- Infectious complications. Mixed bacterial and viral pneumonia (i.e., coinfection) and secondary bacterial pneumonia (i.e., superinfection) are the most common infectious complications in influenza. The most relevant etiologic agents are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and group A *Streptococcus*. Less common coinfecting microorganisms include *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis,* and *Escherichia coli*. These secondary infections may cause bacteremia, septic shock or toxic shock syndrome. Although less frequent, invasive pulmonary aspergillosis has been associated with respiratory worsening in influenza cases requiring ICU admission.
- Cardiac complications. Patients infected with influenza are at higher risk of acute myocardial infarction, probably mediated by the effect of the virus over platelet aggregation, and particularly within the first week of the diagnosis [11]. Myocarditis and pericarditis are uncommon.
- Central nervous system involvement. Potential complications of influenza include Guillain-Barré syndrome, Reye syndrome (particularly in children who have been treated with acetylsalicylic acid), seizures, encephalopathy, encephalitis, stroke or acute disseminated encephalomyelitis.

7.3.3 Diagnosis

The diagnosis of influenza can be suspected on the basis of a compatible clinical picture. Microbiological testing should be considered when the results may influence clinical management decisions or public health activity. Thus, in patients presenting during influenza season with uncomplicated illness and no risk factors, diagnosis may be made based on clinical manifestations. However, patients with influenza symptoms and risk factors (children <5 years and adults >65 years of age, pregnant woman, patients who live in nursing homes or long-term care facilities, and people with chronic underlying diseases) or complicated illness (e.g., pneumonia, hospital admission, etc.) require further testing [9]. Patients who present outside of the influenza season may also require further testing, particularly for differential diagnosis with other respiratory virus infections (e.g., SARS-CoV-2).

Microbiological diagnosis of influenza can be made based on molecular assays (nucleic acid amplification tests) and antigen detection assays in nasopharyngeal specimens. Molecular assays are the first-line technique for the diagnosis of influenza. Reverse transcription polymerase chain reaction (RT-PCR) is the most sensitive and specific test, which allows to differentiate between influenza A and B, as well as influenza A subtypes; however, its turnaround time may be up to 8 h. Multiplex

RT-PCR assays are able to detect a great number of virus and bacteria responsible for respiratory infections, which makes differential diagnosis easier. Alternatively, rapid molecular tests may reduce the turnaround time to less than 1 h, allowing differentiation between influenza A and B, but not among influenza A subtypes. Antigen detection assays should be considered as screening tests, since they have a high specificity, but a limited sensitivity. False-negative results are frequent and should be interpreted cautiously if used for taking clinical decisions. Viral culture and serologic testing have no role in routine clinical practice [8, 9].

7.3.4 Treatment

Treatment of influenza in outpatients is out of the scope of this chapter. Patients with suspected or confirmed influenza infection who require hospital or ICU admission should receive antiviral treatment as soon as possible, given the potential reduction in mortality, complications, and length of stay [8, 9, 12]. The preferred antiviral agent is the neuraminidase inhibitor oseltamivir (75 mg/12 h) for 5 days, which should be prolonged up to 10 days in severely ill patients. While some centers suggest using higher doses in critically ill patients, this practice is not supported by clinical trials [13]. However, the dose should be adjusted in patients with renal function impairment. Corticosteroid administration to patients with severe influenza is controversial, and a recent systematic review by The Cochrane Collaboration concluded that this therapy may be associated with a greater risk of death [14]. Beyond antiviral therapy, the physician must provide symptomatic relief, general supportive therapy (including ICU admission), and any required strategy to prevent complications.

7.3.5 Importance in Intensive Care Medicine

Although most patients with influenza have an uncomplicated disease, a significant proportion are at high risk of severe complications which may require ICU admission, including ARDS, infectious complications and sepsis, cardiac complications, and neurologic involvement. Although early administration of a neuraminidase inhibitor (oseltamivir) may reduce the burden of disease in severely ill patients, supportive measures remain the cornerstone of treatment. Both seasonal and pandemic influenza may overwhelm healthcare systems and ICUs.

7.4 Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)

On December 30, 2019, the municipal health commission of the city of Wuhan, China, alerted about some few cases of unexplained pneumonia. On March 11, 2020, the World Health Organization (WHO) declared SARS-CoV-2 infection as coronavirus disease 2019 (COVID-19) pandemic. Since then, the virus has spread globally causing millions of deaths. After three years from the beginning of the COVID-19

pandemic, several new cases are still affecting the global community and the pandemic is far from being over. As of September 7, 2022, the WHO reported 603,711,760 confirmed cases, 6,484,136 deaths, and 12,540,061,501 vaccine doses administered [15]. Vaccination campaigns have been implemented, and COVID-19 vaccines have demonstrated good efficacy at preventing subjects from getting severe and dying. This protection seems to persist against the new and more transmissible variants (e.g., delta) and over time. However, inequity persists for accessing to COVID-19 vaccines, with less than 3% of doses in low-income countries such as those in the African region. This inequity in providing access of sufficient doses of vaccines to low- and middle-income countries is prolonging the pandemic [16].

7.4.1 Virology

SARS-CoV-2 is an RNA virus with envelop, belonging to the *Betacoronavirus* genus. Coronaviruses belong to the *Coronaviridae* subfamily *Orthocoronaviridae*, and four genera Alpha, Beta, Gamma, and Delta-coronaviruses [17]. The main characteristics of coronaviruses are their ability to mutate, which results in ecological diversity, and the ability to infect and readily adapt to various hosts [17].

The genome of SARS-CoV-2 is composed by 70% of two open-reading frames (ORF-1a and ORF-1b) with nonstructural protein sequences responsible of differences in translation [18]. Between the ORFs, two peptides are encoded and processed to produce nonstructural proteins involved in replication, transcription, and innate immune response (pp1a and pp1b) [18]. The remaining part of the genome encodes for four structural proteins: the spike (S), envelope (E), membrane glycoproteins (M), the nucleocapsid protein (N), and several accessory proteins. The N protein is phosphorylated and directly binds to viral RNA; the E glycoprotein is involved in the maturation and pathogenesis of coronaviruses; and the M glycoprotein is involved in viral assembly and composes the shape of the viral envelope.

SARS-CoV-2 binds to the S subunits and recognizes angiotensin-converting enzyme (ACE) 2 from the renin-angiotensin-aldosterone system (RAAS), binding to its receptor, and fusing the membrane while activating entry-proteases (including TMPRSS2) and cathepsins B and L. SARS-CoV-2 enters the host cells and reduces surface tissue expression of ACE2, also inhibiting the RNA expression. Several cells express the ACE2, including lungs, gastrointestinal, neuronal, and others. Once entered into the cells, SARS-CoV-2 replicates and the ORFs produces two proteins which, in turn, release sixteen non-structural proteins that are implied in proteolytic processing, RNA synthesis, RNA proofreading, and RNA modification [17] (◘ Fig. 7.1). At this point, the host immune response against the virus is activated, with the recruitment of neutrophils, and the innate cells with the release of cytokines. Antigen-presenting cells recognize viral antigens and present to the local lymph nodes, activating T helper cell response, and memory B cells to secrete antibodies [17]. Upon infection, SARS-CoV-2 acts by (1) direct damage to the cells (including endothelial cells), (2) dysregulation of inflammatory-immune response, (3) ACE2 downregulation with dysregulation of the RAAS system, and 4) fibrosis [17].

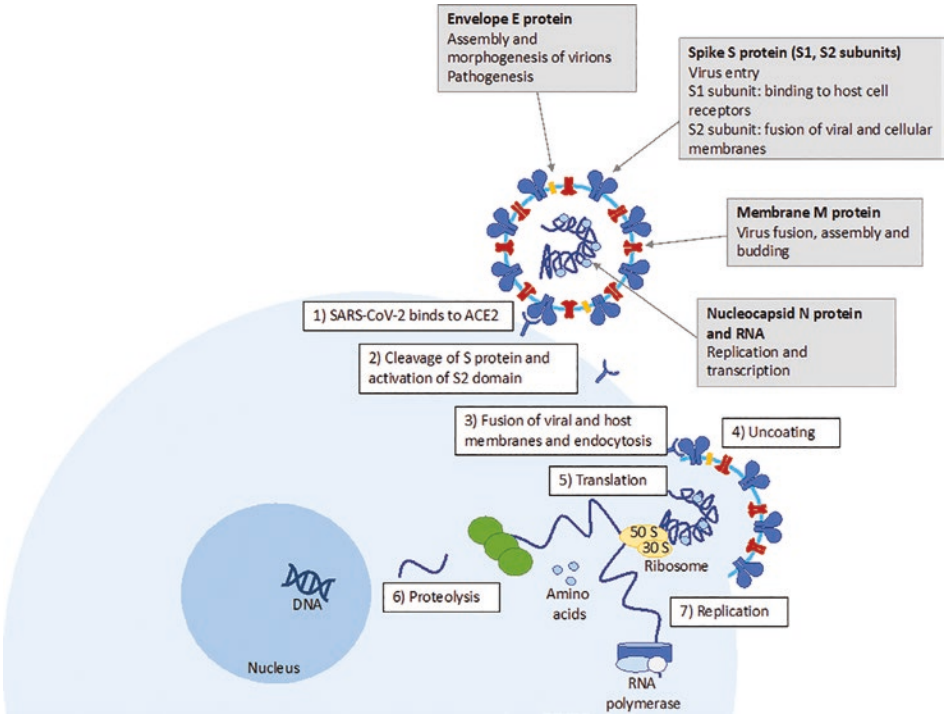

Fig. 7.1 SARS-CoV-2 structure and pathogenic mechanism. *ACE2* angiotensin converter enzyme-2, *SARS-CoV-2* severe acute respiratory syndrome coronavirus-2, *RNA* ribonucleic acid, *DNA* deoxyribonucleic acid

Clinical Presentations and Diagnosis

The respiratory tract represents the primarily affected system during SARS-CoV-2 infection. After entering via ACE2, SARS-CoV-2 infects various cell types of the upper respiratory tract (mucosal membranes, alveolar epithelial cells, and nasal surface), therefore disseminating from the upper to the lower respiratory tract and the systemic circulation across a large surface area of the lungs and vascularization [18]. Symptoms of SARS-CoV-2 infection include mild respiratory illness with fever, cough, and, in most severe cases, ARDS and possible multiple-organ dysfunction [19]. Gastrointestinal manifestations of COVID-19 are the second most common symptoms, including abdominal pain, nausea, diarrhea, and vomiting, as well as possible biliary and liver involvement, with high potential for gut microbial dysbiosis that is associated with unfavorable outcome [19]. COVID-19 critically ill patients may also manifest cardiovascular

symptoms that ranges between 7 and 22% in patients admitted to the Intensive Care Unit (ICU). Cardiovascular symptoms are more often in patients with preexisting cardiovascular comorbidities such as hypertension and who are older [19]. Typical manifestations include acute cardiac injury, reduced ejection fraction, increased levels of troponins, heart attack, deep venous thrombosis, and thromboembolic complications [19]. Additionally, the activation of coagulation and proinflammatory cascades may play a key role in coagulation derangements in COVID-19. Kidney injury has been frequently reported in patients admitted to the ICU for COVID-19. Autopsy results revealed possible proximal tubular injury, erythrocyte aggregation and obstruction of peritubular capillary loops, interstitial edema, and inflammatory infiltrates [19]. The glomerular involvement is typical of those patients with preexisting renal comorbidities. Finally, neurological manifestations of COVID-19 include ischemic stroke (pooled prevalence 2.8% in patients admitted to ICU) [20], delirium (24.3%), central nervous system hemorrhages (intracranial, subarachnoid), and peripheral manifestations like Guillain Barre syndrome [20].

Other minor manifestations include cutaneous involvement and endocrinological diseases [19]. Finally, long-term symptoms are frequently encountered in patients who are discharged from the hospital, even some months after the acute illness, which are associated with poor functional outcome [21, 22].

Given the possible involvement of multiple organs and systems by SARS-CoV-2, monitoring and diagnosis of patients who are critically ill is multifactorial. First, to confirm diagnosis, a polymerase chain reaction molecular test for SARS-CoV-2 infection on nasopharyngeal swab should be carried out. Second, a blood gas analysis, with the assessment of arterial partial pressure of oxygen/fraction of inspired oxygen ratio together with the clinical examination, can help for classification of severity of acute hypoxemic respiratory failure. Third, a complete assessment of blood exams including bilirubin levels, aspartate aminotransferase and alanine aminotransferase, and y-glutamyl transferase can help identifying gastrointestinal manifestations [18]; markers of coagulation disorders (D-dimer, fibrinogen, von Willebrand factor, platelets, international normalized ratio, prothrombin, activated prothrombin time (aPTT) to monitor daily can help in excluding thrombotic or hemorrhagic complications; kidney function can be assessed using creatinine and electrolytes balance [18, 23]; while opportunistic infections can be promptly detected with C-reactive protein, procalcitonin, white blood cells count, and microbiological samples). Fourth, computed tomography (CT)-scan that may help in the identification of the severity of disease and possible lungs phenotypes and exclude possible thromboembolic and other systemic complications [19]. If not available, chest X-ray and lung ultrasound can be considered as alternatives, although with lower sensitivity and specificity [24, 25]. The use of multimodal neuromonitoring systems has been suggested for the identification of possible neurological complications at the bedside, before proceeding with a CT scan or magnetic resonance images [26].

7.4.2 Treatment and Prognosis

Treatment of critically ill patients with COVID-19 is supportive and pharmacological. Supportive treatment includes the sustain of multiorgan function while limiting harms. Mechanical ventilation can be either noninvasive or invasive, according to the severity of acute hypoxemic respiratory failure, lungs' function compromise, and patient's need. Noninvasive mechanical ventilation ranges from low-flow oxygen to high-flow nasal oxygen, continuous positive airway pressure, and noninvasive support assisted by the ventilator, administering oxygen or even positive end-expiratory pressure (PEEP) through different interfaces including helmet, full-face mask, or nasal probes. Patients who fail noninvasive ventilation should be promptly identified and endotracheally intubated [27]. Invasive mechanical ventilation setting should follow the criteria of lung protective mechanical ventilation, using low tidal volumes (4–6 mL/kg of predicted body weight, moderate-high PEEP levels according to the severity, recruitment, and hemodynamic status of the patient, plateau pressure < 27 cmH_2O, and driving pressure < 13 cmH_2O). Rescue strategies can be also considered, including prone positioning, recruitment maneuvers, neuromuscular blockers, inhaled vasodilators, and extracorporeal membrane oxygenation (ECMO) [27]. Pharmacological therapies for patients who are critically ill include intravenous corticosteroids that can be associated (or not) with remdesivir, tocilizumab (or sarilumab), and baricitinib (or tofacitinib) [28]. Other management principles include a conservative management of fluids, nutritional support, stabilization and sustain of hemodynamic status, and treatment of eventual opportunistic infections.

7.4.3 Importance in Intensive Care Medicine

The COVID-19 pandemic has devastated worldwide healthcare systems as well as human health and wellbeing. Prevalence of COVID-19 infection and fatality have extensively varied since the onset of the pandemic. Despite advances in research, rapid implementation of vaccines, and effective therapeutics, the pandemic is still far from being over, especially in low-middle-income countries. Several trials testing potential effective therapeutics are still ongoing, as well as studies investigating the real impact of COVID-19 on organs' disease, rehabilitation, and clinical outcome. Further research is warranted to understand how to effectively guide future investment and obtain more preparedness for future pandemics.

7.5 Herpesviruses Family

Besides immunosuppressed patients after organ or stem cell transplantation, critically ill patients in the Intensive Care Unit represent the largest risk group for infections with viruses. DNA viruses of the herpes group (herpes simplex virus, varicella zoster virus, and cytomegalovirus) as well as the respiratory syncytial virus (RSV) and the influenza virus are responsible for most systemic infections here [29]. Further characteristics of herpesviruses are depicted in Table 7.1.

Table 7.1 Herpesviruses responsible for pneumonia in immunocompromised patients

Virus type	Source	Extra-respiratory manifestations	Diagnosis
HSV (HSV-1, HSV-2)	Donor transmission to transplant recipient Reactivation in T-cell defects	Skin and genital eruption Encephalitis, esophagitis, Keratitis	PCR (blood, BAL, tissue) Tissue culture Serology Histopathology
VZV	Donor transmission to transplant recipient Reactivation in T-cell defects	Varicella, herpes zoster Encephalitis, cerebellitis, hepatitis, myelitis Herpes zoster ophthalmicus	PCR Direct fluorescent antibody testing Viral culture Histopathology
CMV	Donor transmission to transplant recipient Reactivation in T-cell defects	Esophagitis, gastritis, colitis Retinitis, encephalitis, myelitis, polyradiculopathy Neutropenia	PCR (blood, BAL) Histopathology Serology

HSV herpes simplex virus, *VZV* varicella–zoster virus, *CMV* cytomegalovirus, *PCR* polymerase chain reaction, *BAL* bronchoalveolar lavage, *CSF* cerebrospinal fluid, *EIA* enzyme immunoassay

7.5.1 Herpes Simplex Virus (HSV)

Most primary infections with HSV-1 and HSV-2 occur in apparent healthy individuals, with mostly genital or oral manifestation. Generally, infections with HSV-1 are more common than HSV-2 [30]. Local and systemic inflammation, immunosuppression among various others can trigger reactivation, resulting in detection of HSV in the oropharyngeal tract in 20–50% of ICU patients. After about 7 days of invasive ventilation, HSV is detectable in the deeper airways in 20–65% of patients. Today, the technique of so-called quantitative real-time (rt) PCR is used to diagnose HSV-1 and -2 infections. A positive sample of HSV-1 or -2 DNA cannot naturally distinguish between a primary infection and a reactivation. In individual cases in critically ill patients, serological methods enable the detection of type-specific IgG antibodies on the basis of the respective glycoproteins or allow the documentation of a seroconversion. A study with invasively ventilated patients with HSV reactivation showed a twice as high mortality risk compared to patients without detection of HSV [30, 31]. The evaluation of the detection of herpes simplex virus in patients requiring intensive care is often problematic: should virus detection be considered a mere colonization or a relevant infection? The studies are correspondingly inhomogeneous: Brenner et al. showed a poorer outcome in sepsis patients with a high viral load (>108 copies/mL) compared to patients with a lower viral load (<108 copies/mL) [32]. Schuirer et al. were able to show a better outcome in patients with ventilator-associated pneumonia (VAP) with a high detection of HSV (>105 copies/mL) in the BAL when they were treated with acyclovir [33]. On the other hand, in a placebo-controlled study by Luyt et al., ventilated patients with oropharyngeal evidence of

HSV were given antiviral therapy for 14 days. However, there was no significant difference in the outcome and number of ventilation days between the groups [30]. In critically ill ICU patients who have no other causes of pulmonary deterioration, the detection of a high viral load in the BAL may represent a relevant pathogenic factor and should be treated accordingly.

7.5.2 Varicella Zoster Virus (VZV/HHV-3)

The varicella zoster virus (VZV) also belongs to the herpesvirus family (human herpesvirus 3, HHV-3). Laboratory diagnostics of acute and recurrent VZV infections are now directed by nucleic acid amplification methods (PCR). In general, the detection of antibodies enables the differentiation between primary infections and reactivations, but are often inconsistent in immunosuppressed patients and should therefore be evaluated with caution [34]. Immunocompromised individuals, patients with a history of cancer, smokers, and pregnant women are particularly at risk for severe complications. The most frequent and considerably serious complication is varicella pneumonia, which can quickly lead to respiratory failure and ARDS, with a mortality of 50% [34]. Invasive ventilation was required in about 50% of patients within the first two days after admission to intensive care in a multicentric study from France. Three days before the onset of respiratory symptoms, exanthema could be detected in the majority of patients. The authors found that a therapy with steroids led to a higher rate of superinfections and did not improve outcome. Early treatment with varicella zoster immunoglobulin G could have a favorable effect on severe courses of the disease additionally to acyclovir. Other published complications are CNS manifestations and bacterial superinfections of the skin. Hepatitis, arthritis, or myocarditis occur less frequently.

7.5.3 Cytomegalovirus (CMV/HHV-5)

The cytomegalovirus (CMV) is another herpesvirus (human herpesvirus 5, HHV-5) with a high pathogenicity for immunocompromised individuals. After primary infection, latency occurs in myeloid cells under the control of the immune system. Reactivation can occur under immunosuppressive therapy after organ transplantation or in a state of immune paralysis in sepsis [32]. The diagnosis of a primary CMV infection or reactivation is made by a quantitative determination of CMV DNA in RT-PCR format. However, a negative PCR does not always exclude CMV infection or reactivation in immunosuppressed patients, if other manifestations of the infection are suspected (ophthalmologic, gastrointestinal). The spectrum of CMV-related diseases is broad with retinitis, pneumonia, encephalitis, hepatitis, esophagitis, and colitis being the most frequent [32].

In case of CMV disease, viral load is generally higher compared to CMV infection. Critically ill patients with positive serostatus with sepsis present the highest number of reactivations (in the lungs or blood) at 40% [35]. In numerous observational studies, CMV reactivation was associated with increased morbidity and mor-

tality [32, 36]. However, prophylactic antiviral treatment failed to improve outcome in two recent interventional studies of intensive care patients (CMV positive, critically ill, nonimmunocompromised) [37, 38].

The question of the actual clinical significance of CMV reactivation in nonimmunosuppressed patients therefore remains unanswered. Various antiviral drugs are currently available for the treatment of CMV-related diseases: ganciclovir, valganciclovir, foscarnet, and cidofovir. Alternatively, antibody therapies against CMV are available.

7.5.4 Epstein-Barr Virus (EBV/HHV-4)

Epstein-Barr virus (EBV), also known as human herpesvirus 4 (HHV-4), is a herpesvirus that only infects humans and a few primates. After entering the human body, EBV mainly invades B lymphocytes, T lymphocytes, epithelial cells, and muscle cells. In EBV infection, the virus can become latent (inactive). Critically ill patients are more likely to have activation [39]. Because of viral persistence in the organism, detection of herpesviruses in samples of the lower respiratory tract does not *a priori* proof causality with the underlying disease manifestation. While HSV and CMV have been well documented to cause pneumonia in immunosuppressed patients, the role of EBV in respiratory tract infections is still poorly understood. Despite sporadic reports, EBV was found to be associated with idiopathic pulmonary fibrosis and inflammation [40]. Whether EBV reactivation could cause lung inflammation in critically ill patients has not been clearly studied. Regarding of association of EBV with critical illness, the overall clinical significance of EBV DNA detection in BAL seems to be low.

Take-Home Messages

1. The HIV infects central cells of the human immune system, particularly CD4+ T helper cells, and can be acquired via sexual transmission, parenteral transmission, or vertical transmission.
2. Common clinical presentations of HIV include acute retroviral syndrome (ARS), immune processes related to host responses against chronic viral infection in the absence of antiretroviral therapy (ART), opportunistic diseases, immune reconstitution inflammatory syndrome (IRIS), and generalized lipodystrophy syndrome. The leading causes of ICU admission in HIV-infected patients are bacterial sepsis and exacerbation of chronic comorbidities.
3. HIV screening should be performed with a fourth-generation antigen/antibody combination immunoassay that detects HIV-1 and HIV-2 antibodies (IgG and IgM) and HIV-1 p24 antigen. Current guidelines recommend that all patients with acute or early HIV initiate ART as soon as feasible. ART should be continued in HIV-infected patients who were on therapy prior to ICU admission, but an individualized approach to initiation should be used in ART-naive patients in this scenario.

4. Influenza and SARS-CoV-2 infections are acute febrile diseases primarily affecting the respiratory system and are able to produce pandemics. The clinical presentation may range from uncomplicated illness to life-threatening complications (pneumonia, acute respiratory distress syndrome, sepsis, cardiovascular complications, etc.).
5. The first-line technique for the diagnosis of influenza and SARS-CoV-2 is molecular assays (PCR). Patients requiring ICU admission should receive general supportive therapy and specific therapy according to the type of infection (oseltamivir in influenza or intravenous corticosteroids ± remdesivir ± monoclonal antibodies in SARS-CoV-2 infection).
6. The herpesviruses family plays an important role in the ICU, producing encephalitis, pneumonia, gastrointestinal involvement, and skin lesions. Although many of these manifestations occur in immunosuppressed patients, these viruses may reactivate in patients with a state of immunoparalysis, in which they could be associated with unfavorable outcomes.

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Challenges in Infection Management in the Immunocompromised Patient: A Case Report

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Contents

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Learning Objectives

- Recognize that immunocompromised patients have increased risk of infections. Such risk is related to the kind of underlying immune defect which carries variable susceptibility to different pathogens.
- Understand that infections in immunocompromised patients are more severe and carry higher mortality risk.
- Be aware that infections in immunocompromised patients may be multiple, with atypical findings and clinical courses.
- Perform a more in-depth search for opportunistic infections as, in these patients, prompt execution of diagnostic methods is important to guide subsequent patient management.
- Review two common opportunistic infections - *Pneumocystis jirovecii* and *Cytomegalovirus*.

8.1 Introduction

Over the past decades, a myriad of immunosuppressive agents have been developed, greatly improving the prognosis of a wide range of diseases. However, these novel agents are not without complications and the incidence of serious infections is high. These patients often present a more aggressive clinical course, may require ICU admission, and have a higher mortality rate.

These patients are susceptible not only to common community-acquired infections but also to unusual and opportunistic microorganisms. These opportunistic infections can be the cause for ICU admission or may complicate the ICU stay. Outcomes can be optimized by early diagnosis and aggressive treatments.

The immunosuppressive state comprises a wide spectrum of defects, ranging from humoral response, neutrophil quantity/function, and B-cell or T-cell immunity, and the same patient can have several defects. Additionally, different immunity defects confer variable risk of different opportunistic infections [1].

Pneumocystis jirovecii pneumonia (PJP) is a common opportunistic infection among immunocompromised patients, and several immunosuppressive agents increase the risk of *Pneumocystis jirovecii* (PJ) infection. *Cytomegalovirus* (CMV) infection is another common cause of pneumonia in immunocompromised hosts, and CMV coinfection can be observed in patients who are infected with other pathogens.

Previous studies have reported that pathogenesis and prognosis of pulmonary CMV infection with PJP in non-HIV patients is poorly understood, but suggest that CMV infection can alter the host's immune response by suppressing the function of helper T-cells and antigen-presenting cells, which are essential for achieving PJP resolution [2].

Lung imaging with CT scanning and broncho-alveolar lavage (BAL) are useful tools in diagnosing and guiding therapy, considering infection with these pathogens in immunocompromised patients can present minimal signs and symptoms and/or atypical features in unusual locations.

In the deteriorating immunocompromised patient, it is of the utmost importance to promptly collect all possible microbiological samples for analysis and initiate antimicrobials including broad-spectrum antibiotics covering most gram-negative and gram-positive microorganisms, including multidrug resistant coverage according to local ecology, as well as other agents covering other suspected infections (viral, fungal, or parasitic).

Case Presentation

A 40-year-old, caucasian, female patient presented to the Emergency Department due to worsening fever, myalgias, and fatigue for the last 5 days.

She has a previous history of autoimmune thyroiditis and polymyositis, diagnosed 8 years before, with positive anti-Jo1 and anti-Ro52 antibodies and a concordant muscle biopsy. Three months prior to the current visit, she had a mild SARS-CoV-2 infection, despite three doses of an mRNA COVID-19 vaccine. She had also been vaccinated against the seasonal flu.

The patient was chronically medicated with levothyroxine 100mcg id, pantoprazole 40 mg id, azathioprine 75 mg id, prednisolone 40 mg id, etoricoxib 60 mg id, and daily calcium + vitamin D supplementation.

Her past few months had been troublesome with aggravating myalgias, muscle weakness and fatigue, for which her attending Rheumatologist prescribed prednisone 1 mg/kg plus azathioprine 75 mg id, without complete remission of the symptoms. Following the lack of a favorable response, the patient was given 2 doses of intravenous rituximab 375 mg/m^2, which was last administered 3 weeks prior to her current visit to the emergency department.

She had been diagnosed with H1N1 Influenza virus last week due to upper respiratory symptoms and had a chest CT scan demonstrating bilateral upper lobe ground-glass opacities and, in the right lower lobe, an area with heterogeneous consolidation, septal thickening, and traction bronchiectasis. That day, she was on her fifth day of oseltamivir 75 mg bid (plus acetaminophen and ibuprofen as needed) but with worsening symptoms.

On physical examination, the patient was alert, oriented, and cooperative, mildly polypneic with 22 breaths/min, SatO2 88% on room air, axillary temperature 38.4 °C, blood pressure 111/66 mmHg, heart rate 110 bpm, and pulmonary auscultation revealed fine, disperse crackles across both pulmonary areas, with no other changes. O_2 saturation improved to 98% with 2 L/min of supplementary oxygen.

Blood samples' analysis revealed severe neutropenia (<100/μL) and lymphopenia (~300/μL), without anemia or thrombocytopenia, a C-reactive protein of 5.0 mg/dL, with normal renal and liver tests. Chest radiograph revealed diffuse bilateral patchy infiltrates. The patient was admitted to the general ward after collection of blood cultures and broad-spectrum antibiotic therapy with piperacillin/tazobactam 4.5 g qid was started while oseltamivir was maintained.

Less than 24 h after admission, the patient presented worsening respiratory failure, requiring increasing amounts of FiO_2 to achieve O_2 saturation >88% and was referred to the Intensive Care Unit (ICU).

8.2 Investigations

Right before admission to the ICU, we performed a contrast-enhanced chest CT, which revealed diffuse bilateral pulmonary opacities, with ground-glass areas and interstitial thickening, suggestive of extensive bilateral pneumonia and excluded pulmonary embolism. Compared to the CT scan 5 days prior, we could observe a great increase in pulmonary opacities, which were prominent in all lung areas (Fig. 8.1).

A flexible fiberoptic bronchoscopy with broncho-alveolar lavage was performed in the first 24 h of ICU admission, in order to collect a deep, aseptic microbiological sample, which was tested for bacterial and mycobacterial analysis, as well as nucleic acid detection of *Herpes Simplex Virus, Epstein-Barr Virus* (EBV), *Cytomegalovirus,* and *Pneumocystis jiroveci*.

Peripheral blood smear confirmed the absence of granulocytes and of immature forms, however, to better characterize the agranulocytosis, a bone marrow aspirate was performed. Marrow smears revealed the presence of several atypical hyperbasophilic cells, with features of activation and no excess blasts or dysplasia. Serum IgG dosing was compatible with hypogammaglobulinemia.

Blood and urinary cultures were repeated and *Streptococcos pneumoniae* and *Legionella* spp. urinary antigens were negative. Human immunodeficiency virus 1 and 2 screening test was negative.

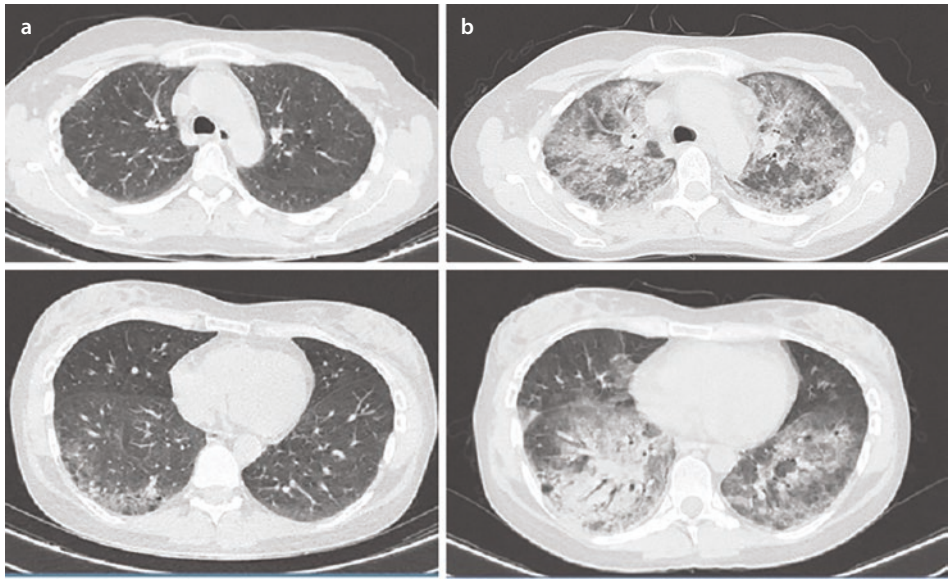

Fig. 8.1 CT scan images, 5 days apart, of the upper lobe (upper images of panels **a** and **b**) and lower lobe (lower images of panels **a** and **b**). The first CT scan (panel **a**) demonstrates bilateral upper lobe ground-glass opacities and, in the right lower lobe, an area with heterogeneous consolidation, septal thickening, and traction bronchiectasis. The second CT scan shows aggravating lesions, with diffuse bilateral pulmonary opacities, with ground-glass areas and interstitial thickening

8.3 Differential Diagnosis

Upon ICU admission and following the chest CT images, which were suggestive of *crazy paving pattern*, we considered several diagnosis, particularly **acute respiratory distress syndrome (ARDS) secondary to H1N1 influenza** virus infection, which was probable considering the patient had been diagnosed 5 days earlier, despite being under oseltamivir. **Bacterial superinfection** was also a likely cause, being a frequent finding in patients with Influenza, particularly in an immunocompromised patient with severe neutropenia.

Opportunistic infections were also probable diagnosis, which are more frequent in immunocompromised patients, namely ***Pneumocystis jiroveci*** and ***Cytomegalovirus***, and can present with progressive respiratory failure. Common CT findings in cases of PJP are ground-glass opacities, predominantly apical, *mosaic pattern*, *crazy-paving pattern*, and cystic changes. CMV pneumonia typically includes poorly defined ground-glass opacities, small nodules, *tree-in-bud pattern*, the *halo sign*, mainly in the middle and lower lung fields, while thickening of the bronchovascular bundles, and pleural effusion are rare.

Pulmonary involvement by polymyositis was also a possibility, considering the recent flare of the disease and the presence of what can be interpreted as *nonspecific interstitial pneumonia pattern* on the first CT scan, with septal thickening, traction bronchiectasis, and ground-glass opacities.

8.4 Treatment

At ICU admission, and considering the poor outcomes of immunocompromised patients with invasive mechanical ventilation, a trial of high flow nasal oxygen (HFNO) was attempted, with a flow rate which was rapidly titrated up to 60 L/min, with good patient tolerance, and an initial FiO_2 of 70%.

Recombinant granulocyte-colony-stimulating factor (filgrastim 30 MUI id) was administered to try to expedite recovery from neutropenia, and antibiotic therapy was escalated with the association of vancomycin continuous infusion, after a loading dose 25 mg/kg, to the previously prescribed piperacillin/tazobactam, which we administer as 18 g/day continuous infusion. Oseltamivir dose was doubled to 150 mg bid, assuming ARDS secondary to H1N1 influenza. Initial choice of antibiotics was based on a very low prevalence of carbapenemases-producing Enterobacteriaceae (CPE) but a relatively high prevalence of methicillin-resistant *Staphylococcus aureus*, in our institution.

Considering our hypothesis of PJP and being cautious of trimethoprim/sulfamethoxazole (TMP/SMX) marrow toxicity, we empirically started atovaquone 750 mg bid, until the BAL could be safely performed. Metilprednisolone was also administered at a dose of 1 mg/kg, keeping in mind a potential role as an adjuvant to ARDS treatment, *Pneumocystis jiroveci* treatment, and the potential pulmonary involvement by polymyositis.

The patient remained polypneic, with a respiratory rate around 30 breaths per minute, and in the first hours of HFNO, FiO_2 was rapidly escalated to 100% in order to maintain $SatO_2$ > 90% and the arterial blood gas analysis demonstrated PaO_2/

FiO_2 ratios consistently <100 mmHg. The decision was made to intubate and invasively mechanically ventilate the patient, using a protective lung strategy (tidal volume 6 mL/kg of ideal body weight, plateau pressure < 30cmH_2O, driving pressure < 15cmH_2O, respiratory rate < 30 breaths per minute).

Following evidence of hypogammaglobulinemia (serum IgG < 400 mg/dL), intravenous IgG was administered as replacement therapy.

On the third day of admission, neutrophil count was >1000/μL and microbiologic analysis of the BAL was positive for CMV, PJ, and EBV. We switched atovaquone for TMP/SMX 15 mg/kg/day and started ganciclovir 5 mg/kg bid, pending the serum CMV viral load, which later was confirmed positive. The patient completed a 10-day course of oseltamivir.

8.5 Evolution, Outcome and Follow-up

The patient was supported with invasive mechanical ventilation (IMV) with a protective ventilation strategy, with a need to accept permissive hypercapnia to keep driving pressure below 15 cmH_2O, as the patient presented very low compliance, with steady improvement of oxygenation parameters. A trial of prone position was attempted to optimize ventilation and oxygenation, in the first days of IMV, without significant improvement in ventilatory parameters. Noradrenaline was required to maintain mean arterial pressure above 65 mmHg and adequate tissue perfusion, at a maximum dose of 0,7 μg/kg/min.

Both sets of blood cultures from admission were positive for *Branhamella catarrhalis*, susceptible to amoxicillin/clavulanate, second-generation cephalosporins, and quinolones, which led us to de-escalate piperacillin/tazobactam and vancomycin combination to ceftriaxone 2 g bid monotherapy, according to the antibiotic susceptibility test. Transesophageal echocardiography excluded endocarditis.

TMP/SMX was maintained for 14 days and steroids were tapered to PJP treatment protocol (40 mg of prednisone equivalent dose bid for 5 days, followed by 40 mg id for 5 days and then 20 mg id for 11 days). After consultation with the attending rheumatologist, we decided to maintain a daily dose of 10 mg of prednisolone to prevent a recrudescence of polymyositis manifestations. Prophylactic TMP/SMX dose was maintained. Ganciclovir was sustained at induction dose for 21 days, until the serum viral load was undetectable, and then switched to daily single dose, as maintenance therapy. Despite the large volumes of fluids required to administer all drugs, it was possible to maintain the patient at an euvolemic state and kidney function remained stable.

Two additional administrations of intravenous immunoglobulin were required to maintain serum IgG > 400 mg/dL.

Despite low nutritional risk (mNUTRIC score 3), adequate nutritional support with enteral feeding and physical rehabilitation, the patient quickly developed extensive critical illness myopathy, which greatly impaired ventilatory weaning and a percutaneous tracheostomy was performed on the 13th day of IMV. Delirium was also apparent from the first days of sedation weaning, which further hampered ventilatory support weaning. Progressive CMV viral load clearance was simultaneous with improvement in chest radiograph, as well as ventilatory weaning.

The remainder of the admission was further complicated by catheter-associated urinary tract infection, with microbiological isolation of *Escherichia coli,* sensitive to ceftriaxone. The patient also presented two episodes of supraventricular tachycardia with hemodynamic instability, requiring synchronized electrical cardioversion.

Finally, on the 24th day of IMV, the patient was able to tolerate periods of spontaneous breathing with oxygen support and on the 41st day of ICU admission the patient was decannulated.

The patient was discharged from the ICU after 44 days to the general ward with intensive physical rehabilitation support and was discharged from the hospital after 64 days. The patient is currently alive and managing well, fully autonomous in her activities of daily life, however, with symptoms that limit some activities.

8.6 Discussion

We present the case of a 40-year-old female patient with polymyositis, under three immunosuppressive agents, with a recent diagnosis of H1N1 influenza, under oseltamivir, with progressive respiratory failure, severe neutropenia, and CT findings of bilateral pulmonary opacities, with diffuse ground-glass areas, interstitial thickening, without significant pleural effusion.

Although not specific and rarely diagnostic, imaging scans are very useful in guiding differential diagnosis, subsequent investigations, and initial therapy. In our case, initial CT findings could well be in the context of H1N1 influenza, but the progressive changes are more in favor of ARDS, with bacterial superinfection and/or opportunistic infection.

We started broad-spectrum antibiotics covering most gram-negative and gram-positive microorganisms, based on our local ecology. Arguably, this strategy could be different in other settings of CPE prevalence. We also added atovaquone and steroids, empirically, thinking about ARDS, PJP, and the eventual pulmonary involvement by polymyositis. In fact, this patient was also severely neutropenic at admission. Pure agranulocytosis is a rare side effect of azathioprine, and there are some cases associated with rituximab. Perhaps overcautiously, we performed a bone marrow aspirate to exclude other causes of agranulocytosis and to safely institute G-CSF therapy. Not surprisingly, this patient also had secondary hypogammaglobulinemia. We started replacement therapy to keep IgG levels >400–500 mg/dL, in light of evidence that may reduce infectious complications [3]. In this regard, infectious prophylaxis, particularly PJP and viral reactivation prophylaxis, are recommended to prevent severe infectious complications. Our patient was not under such prophylactic therapy, and a recent study reports it may be underprescribed [4].

Indeed, using quantitative real-time PCR, we identified significant copies of both PJ and CMV in the BAL, and a high serum CMV copy number. The detected pulmonary CMV infection could represent CMV reactivation, rather than CMV pneumonia; however, two previous studies found that development of severe ARDS and need for mechanical ventilation was more common in the CMV/PJP coinfection group [2, 4]. Another study found that higher CMV DNA loads were significantly associated with mortality and that many of the patients exhibited severe hypoxemia, which precluded the use of lung biopsy to diagnose CMV pneumonia. We also did not perform

lung biopsy considering such risks; nevertheless, we treated with ganciclovir and observed a favorable clinical evolution concomitant with CMV viral load clearance.

In summary, this case demonstrates that in severely immunocompromised patients, infections with typical and atypical microorganisms can occur at the same time, further complicating the disease course, making prompt institution of therapy of the utmost importance.

Take-Home Messages

- Immunocompromised patients have increased risk of infections, which is related to the kind of underlying immune defect.
- Opportunistic infections are frequent in this setting but may be difficult to diagnose and treat; they can be the cause for intensive care admission or may arise during ICU stay.
- Imaging studies are important to guide further investigations and can provide clues to the underlying etiology.
- Mortality risk is high, which warrants prompt early diagnosis and aggressive treatments.
- PJP should be suspected in the immunocompromised patient, particularly if CT findings are compatible and the patient presents an insidious clinical course.
- CMV pneumonia/reactivation should be suspected particularly in cases of severe hypoxemia and compatible CT changes.
- PJP and CMV infections may co-exist in the same patient.

Summary

Immunosuppressive agents, although greatly improving prognosis of a wide range of diseases, carry significant risk of infection of both typical and atypical microorganisms. Immunocompromised patients are at increased risk of such infections and exhibit a more aggressive clinical course with higher mortality.

Pneumocystis jirovecii and *Cytomegalovirus* are common opportunistic infections that can cause pneumonia in immunocompromised hosts and coinfection may occur. *Pneumocystis jirovecii* prophylaxis is recommended to prevent severe infection.

We present the case of a 40-year-old, caucasian, female patient, with a history of autoimmune thyroiditis and polymyositis for which she was recently medicated with steroids, azathioprine, and rituximab. She presented to the emergency department on her fifth day of H1N1 influenza infection, under oseltamivir 75 mg bid, diagnosed following upper respiratory symptoms. On physical examination, the patient was alert, oriented, and cooperative, polypneic, $SatO_2$ 88% on room air, febrile, tachycardic and normotensive with fine, disperse crackles across both pulmonary areas on pulmonary auscultation. The patient was severely neutropenic and had a C-reactive protein of 5.0 mg/dL.

Less than 24 h after admission, the patient presented worsening respiratory failure requiring ICU admission and ultimately invasive mechanical ventilation, despite initial piperacillin/tazobactam plus oseltamivir therapy. CT scan revealed diffuse bilateral pulmonary opacities, with ground-glass areas and interstitial thickening. Hypogammaglobulinemia was identified, and replacement therapy was instituted.

Blood cultures from admission revealed *Branhamella catarrhalis* bacteremia, and a broncho-alveolar lavage was obtained, and a diagnosis of *Pneumocystis jiroveci* pneumonia and *Cytomegalovirus* co-infection with high serum viral load was made. Targeted therapy was started and after some days the patient started to improve from her severe ARDS.

Clinical course was complicated with severe critical illness associated myopathy and delirium which greatly impaired ventilatory weaning, requiring percutaneous tracheostomy. Finally, the patient was discharged from the hospital after 64 days, alive and managing well.

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HIV: Respiratory Insufficiency in an HIV Patient

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Learning Objectives

- HIV should be suspected in any patient presenting constitutional symptoms or signs of immunosuppression.
- Respiratory insufficiency is the main cause of ICU admissions in HIV patients.
- Decisions to withhold or withdraw life-sustaining interventions can be ethically challenging, and a multidisciplinary approach involving the family is recommended.

9.1 Introduction

HIV infection is a major public health problem worldwide. Although rates of hospitalization have decreased significantly after the advent of antiretroviral therapy, late-stage HIV infections remain a common diagnosis for ICU admission in settings where access to diagnosis, treatment, and specialized care are limited [1]. Acute respiratory failure is the most common cause for ICU admission in HIV patients, and it is usually associated with either an unknown diagnosis or lack of proper treatment. In patients with advanced immunosuppression, severe opportunistic infections, bacterial sepsis, and tuberculosis remain common etiologies [2]. Over the past decades, noninfective respiratory complications, such as structural lung disease and malignancy, have emerged as frequent causes of critical illness in people living with HIV, consequences of a longer life expectancy associated with lifetime low-level inflammation, coinfections, and sequelae of past infections and pharmacological toxicity [1, 2].

Case Presentation

A 31-year-old Guinean woman living in Portugal for the past year presented to the emergency room (ER) with a one-month history of asthenia, adynamia, night sweats, low fever, and dry cough. She had no relevant medical history, no previous medical records were available, and she could not recall the last time she visited a medical center.

At admission, she was febrile and tachycardic, but normotensive and eupnoeic without any oxygen support (SpO_2 99%). Thoracic radiography revealed diffuse bilateral infiltrates with a left lower lobe condensation. Laboratory tests showed a microcytic anemia, an elevated C-reactive protein, and a positive rapid HIV test. A thoracic CT scan was performed to characterize lung parenchyma: it showed several small consolidative foci scattered over both lung fields and ground-glass opacities present in the lower and upper left lobe and middle right lobe. Miliary pattern was absent. Nasopharyngeal swab for influenza A, B and SARS-CoV-2 and urinary antigen tests for *Pneumococcus* and *Legionella* were all negative. Blood, urine, and sputum samples were collected (including Ziehl–Neelsen stain) with inconclusive results.

The patient was moved from the ER to a medical ward. On day 2, she developed type 1 respiratory insufficiency, and the infectious diseases department was consulted. Empiric treatment with piperacillin-tazobactam, trimethoprim-sulfamethoxazole, and fluconazole was

advised after obtaining new microbiological specimens. She was then submitted to a bronchoalveolar lavage (BAL) on day 3, but no relevant isolations were made.

Despite all measures taken, the patient remained febrile and developed a progressively worsening respiratory failure, acute kidney injury (AKIN 3), and a hematologic dysfunction with thrombocytopenia. She was transferred to an Intensive Care Unit (ICU) and intubated due to respiratory exhaustion on day 6. By day 8, she evolved to septic shock complicated with acute respiratory distress syndrome (ARDS) (P/F ratio 120). A trial of prone ventilation was attempted without any improvement. Refractory acidemia with unsafe ventilator settings (plateau pressure 33 cmH_2O, driving pressure 16 cmH_2O) led to a referral for extracorporeal carbon dioxide removal ($ECCO_2R$) therapy in our tertiary center.

9.2 Investigations

Relevant investigations and complementary tests were divided and paired with the main problems identified at admission:

- Microcytic hypochromic anemia: blood work showed folate deficiency and sickle cell trait.
- HIV: CD3+/CD4+ (helper T cells) 8 Cells/uL, T4/T8 ratio 0.02, and HIV-1 viral load 319,196 copies/mL
- Etiology of respiratory insufficiency (Table 9.1).

Table 9.1 Serologies, PCR assays, and site-specific cultures performed in order to study respiratory insufficiency

Respiratory insufficiency			
Nasopharyngeal swab		Blood	
Influenza A, Ag	Negative	Hepatitis A, Ab	Positive
Influenza B, Ag	Negative	Hepatitis B, HBs Ab	Negative
SARS-CoV-2, PCR	Undetectable	Hepatitis B, HBs Ag	Negative
Urine		Hepatitis B, HBe Ag	Negative
Urine Culture	Negative	Hepatitis B, HBc Ab	Positive
Streptococcus pneumoniae, Ag	Negative	Hepatitis B, PCR	Undetectable
Legionella pneumophila sg 1, Ag	Negative	Hepatitis C, Ab	Negative
Chlamydia trachomatis, PCR	Undetectable	*Toxoplasma gondii*, Ab IgM	Negative

(continued)

Table 9.1 (continued)

Respiratory insufficiency			
Neisseria gonorrhoeae. PCR	Undetectable	*Toxoplasma gondii*, Ab IgG	Positive
Sputum		Citomegalovirus (CMV), Ab IgM	Negative
Direct exam	Negative for bacteria	Citomegalovirus (CMV), Ab IgG	Positive
Ziehl-Neelsen stain (3 samples)	Negative	EBV, PCR viral load	**Still processing at day 8**
Culture	Negative for bacteria	Herpes Zoster Virus, Ab IgM	Negative
Bronchoalveolar lavage		Herpes Zoster Virus, Ab IgG	Positive
Direct exam	Negative for bacteria	*Cryptococcus neoformans*, Ag	Negative
Ziehl-Neelsen stain (3 samples)	Negative	*Strongyloides stercolaris*, Ab IgM	Negative
Culture	Negative	*Strongyloides stercolaris*, Ab IgG	Negative
Mycobacterium tuberculosis, PCR	Undetectable	*Schistosoma spp*, Ab IgM	Negative
Pneumocystis jirovecii, PCR	Undetectable	*Schistosoma spp*, Ab IgG	Negative
CMV, PCR viral load	**Still processing at day 8**	*Treponema pallidum* Ab, TPHA	Negative
Galactomannan	Negative	Plasmodium, blood smear	Negative
		Culture	Negative

9.3 Differential Diagnosis

Differential diagnosis is summarized in Table 9.2.

Table 9.2 Differential diagnosis of respiratory insufficiency in HIV patients

Infectious		Non-Infectious
Bacterial	**Streptococcus pneumoniae, Haemophilus influenza,** Staphylococcus aureus, Group B Streptococcus, Moraxella catarrhalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Legionella spp., Mycoplasma pneumoniae, Chlamydophila pneumoniae, Rhodococcus equi, Norcardia asteroides, Pasteurella multocida	Lymphocytic interstitial pneumonitis, Non-specific interstitial pneumonia, Illicit drug-induced lung disease, Medication-induced lung disease, Bronchiolitis obliterans, Cryptogenic organizing pneumonia, Sarcoidosis, Foreign body granulomatosis, hemophagocytic lymphohistiocytosis
Fungal	**Pneumocystis jirovecii, Aspergillus, Cryptococcus spp., Candida spp., Histoplasma spp., Coccidioides spp**., Mucorales spp., Scedosporium apiospermum complex, Lomentospora prolificans, Fusarium spp., Trichosporon spp., Geotrichum spp., Aureobasidium spp., Alternaria spp., Curvularia spp., Phialophora spp., Wangiella spp., Cladosporium spp.	
Viral	**Cytomegalovirus, SARS-CoV-2, Influenza,** Parainfluenza, Respiratory syncytial virus, Metapneumovirus, Adenovirus, Herpes Simplex virus, Varicella-Zoster virus	HIV-related neoplasms: Kaposi sarcoma, Non-Hodgkin lymphoma, Primary effusion lymphoma, Lung cancer
Parasitic	**Strongyloides stercoralis, Toxoplasma gondii**	
Mycobacterial	**Mycobacterium tuberculosis,** Mycobacterium kansasii Mycobacterium avium complex	

9.4 Treatment

Treatment was based on the assumption that respiratory failure was due to an infectious cause. Broad-spectrum antibiotic, antifungal, and antiviral covering the most common related infections in HIV patients were administered:

- Piperacillin-tazobactam covering the most common agents for community-acquired pneumonia and later, meropenem and Vancomycin, for multiresistant organisms.
- Trimethoprim-sulfamethoxazole (therapeutic dose) for *P. jirovecii* as well as adjunctive corticosteroids.
- Fluconazole covering *Candida* spp., *C. neoformans,* and *Coccidioides* spp., later changed to Amphotericin B, Flucytosine to include *H. capsulatum* and *Aspergillus* spp.
- Ganciclovir for CMV, HSV, VZV, and EBV.

Shock was managed through organ support with mechanical ventilation and later venous-venous extracorporeal membrane oxygenation (VV-ECMO), renal replace-

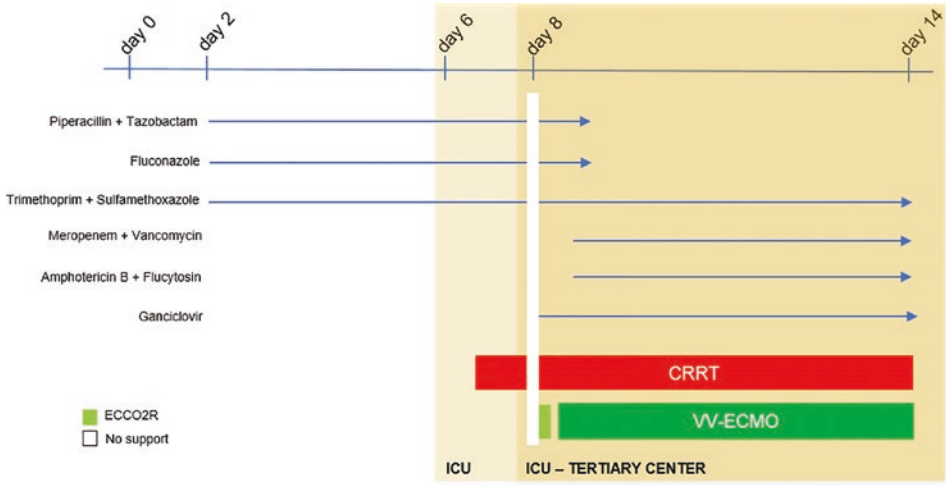

Fig. 9.1 Treatment timeline

ment treatment, vasoactive drugs, and blood transfusions. No highly active antiretroviral therapy (HAART) was initiated during her UCI stay. Antimicrobial therapy timeline is schematized in Fig. 9.1.

9.5 Evolution, Outcome, and Follow-up

Reevaluation after transport to our center showed a multiorgan dysfunction: she was dependent on norepinephrine at a rate of 2 mcg/kg/min, mechanical ventilated with FiO_2 100% (P/F ratio 78), and actively bleeding from insertion sites of the different catheters. Lab work showed a severe acidosis (pH 7.08, pCO_2 80 mmHg, pO_2 78 mmHg, HCO_3 18 mEq/L, and lactate 3.9 mmol/L), an aggravated anemia (Hb 5.9 g/dL), and thrombocytopenia (57×10^9/L platelets). Considering the multiorgan dysfunction and after a long multidisciplinary meeting with the medical staff and family, it was decided that invasive organ support measures would be decremented and that comfort measures would be prioritized. Eight hours later, and after repositioning the patient to a left lateral decubitus as part of the preventive measures for pressure ulcers, SpO_2 improved spontaneously from 70% to 92% and a mean arterial pressure > 65 mmHg was maintained under 1 mcg/kg/h of norepinephrine. Active bleeding was partially controlled with hemostatic absorbent.

After this nonexpected improvement, an extensive rediscussion led to a revocation of the previous decision. Empiric antimicrobial therapy was restarted along with Ganciclovir. Organ support measures were resumed, vasopressin was added, and an $ECCO_2R$ device was combined with continuous renal replacement therapy.

Although the patient exhibited a slight improvement, low-flow $ECCO_2R$ therapy was not enough to compensate for the respiratory acidosis, and support was escalated to VV-ECMO therapy (initially Qb 3 L/min, SGF 1 L/min FiO_2 100%, mechanically ventilated with APRV, Thigh 5″, TLow 0.4″, PHigh 20 cmH_2O, Plow 0 cmH_2O, FiO_2 60%). Infectious diseases department was consulted and given the absence of

any microbiologic isolation and maintenance of shock, a new BAL fluid was collected and analyzed (including a respiratory viral panel, A*spergillus fumigatus*, *Mycobacterium tuberculosis,* and *Pneumocystis jirovecii* PCR), blood culture and serologies repeated, and empiric treatment was escalated to Meropenem, Vancomycin, Amphotericin B, Flucytosine, maintaining Ganciclovir and Trimethoprim | Sulfamethoxazole. Repeated *Cryptococcus neoformans* antigen resulted in low-titer positive: given a first negative test, negative cultures and already directed treatment implemented, cross-reaction was suspected. BAL fluid PCR for CMV and serum PCR for EBV were positive on day 11 (no viral quantification available). Hemodynamic and hematologic instability contraindicated a lumbar puncture and a transport to the radiology department for full-body CT scan.

A total lymphocyte count was also repeated, and it showed a decrease in CD4+ count to 3 cells/uL and an unusually raised total B cells (1014,96 cells/uL). Although not specific, flow cytometry used to assess total lymphocyte count exhibited a separate population of activated B cells, not completely explained by CMV, EBV, or HIV infection. A B-cell lymphoproliferative disorder was suspected, and peripheral immunophenotyping was suggested.

The 11th day was marked by a rising lactate from 1.9 to 3.7 mmol/L, associated with new onset tachycardia, not completely responsive to fluids. By day 12, lactate was 11 mmol/L. Transthoracic echocardiography reported a reduction of cardiac output with a preserved contractility. RV dysfunction was absent. Worsening renal, cardiovascular, and respiratory, hematologic failure made her not eligible for VA-ECMO. Even though there were no obvious signs of oxygenator dysfunction, it was changed without any effect on the patient, who eventually died on day 14.

9.6 Discussion

The HIV epidemic continues to be a major public health issue: since the widespread use of antiretroviral therapy, HIV prevalence has doubled, and there are currently 37.7 million people living with it, two-thirds of whom in the African Region [3]. AIDS remains a common cause of ICU admission in untreated and undiagnosed patients [2]. Diagnosis should be suspected in a patient presenting with constitutional symptoms and social risk factors (for example, an African migrant without easy access to a health care system) [1].

AIDS presentation resembles the early years of the HIV pandemic with an advanced immunosuppression leading to opportunistic infections (OI). *P. jirovecii* remains the most common OI in AIDS and, together with tuberculosis and community acquired pneumonia, accounts for 60–90% of acute respiratory failure in these patients. Severe pneumonia due to CMV, *H. capsulatum,* and *C. neoformans* have also been extensively described and multiple OI may coexist [2].

Our patient did not exhibit any suggestive imaging pattern and microbiological findings were negative at first. Due to the hemodynamic instability, broad-spectrum empiric treatment was maintained, covering all of most common agents. A positive CMV viral load on BAL fluid suggested active viral replication and CMV pneumonitis. Chronic EBV infection and reactivation have been linked to life-threatening lymphoproliferative disorders and hemophagocytic lymphocytosis (HLH) [2]. Serum

viremia and clonal B cell proliferation spotted during flow cytometry were suggestive of malignancy. Whole-body CT scan and blood immunophenotyping would have helped with the diagnosis of malignancy as well as determination of soluble CD25 and triglycerides for the diagnosis of HLH (ferritin 8909,1 ng/mL).

Starting HAART therapy in critically ill patients remains controversial, and no consensus guidelines exist to guide us. Drug interactions, toxicities, and immune reconstitution inflammatory syndrome are valid concerns when dealing with AIDS-related complications, and therapy initiation was delayed [1].

Dysthanasia is a term used to describe the undue prolongation of death with the help of technological means without regard to the person's quality of life (mechanical ventilation, ECMO, extensive pharmacological support, etc.), resulting in a suffered death [1]. End-of-life support represents almost always an ethical dilemma: are we postponing the inevitable? Are we doing more harm than good? And in this case, was it ethical to place the patient in $ECCO_2R$ and VV-ECMO? Decisions to withhold or withdraw life-sustaining interventions can be ethically challenging and a multidisciplinary approach with the medical staff and family should be encouraged. Decisions should always be revalidated after the emergence of new facts, and room for a change should be available.

Take-Home Messages

- HIV should be suspected in any patient presenting constitutional symptoms or signs of immunosuppression.
- Respiratory insufficiency is the main cause of ICU admission in HIV patients.
- Etiology is most commonly from an infectious origin, but noninfectious etiologies may occur.
- *P. jirovecii* is the most common agent in AIDS.
- Multiple opportunistic infections may coexist.
- Starting HAART therapy in critically ill patients remains controversial and no consensus guidelines exist.
- Decisions to withhold or withdraw life-sustaining interventions can be ethically challenging and a multidisciplinary approach is recommended.

Summary

We present a case of a 31-year-old Guinean woman with a one-month history of asthenia, fever, night sweats, and dry cough. An inaugural diagnosis of HIV-AIDS was made at admission. She had no previous medical history. Due to an assumed pneumonia, she developed respiratory failure requiring invasive mechanical ventilation and was transferred to an ICU. No isolations were made at that time. Progressive respiratory insufficiency with refractory acidosis and unsafe ventilation parameters led to the referral to a tertiary center for extracorporeal carbon dioxide removal ($ECCO_2R$).

At our tertiary center, severe multiorgan dysfunction was evident: she was anuric, dependent on norepinephrine at a rate of 2 mcg/kg/min, mechanically ventilated with FiO_2 100%, and actively bleeding. Lab work showed severe acidosis, aggravated anemia, and thrombocytopenia. After a long multidisciplinary meeting with the medical staff and family, invasive organ support measures were decremented and comfort was prioritized.

Unexpectedly, 8 h after and when repositioning the patient, spontaneous improvement of SpO_2 and mean arterial pressure were noted. Active bleeding was also partially controlled with hemostatic absorbent. Previous limiting decision was revoked, and the patient was placed on $ECCO_2R$ and then escalated to VV-ECMO.

Specimen collections were repeated. A CMV was isolated from BAL fluid, a weak positive antigen for cryptococcosis and EBV viral load were perceived in the blood. Empiric treatment started at our ICU already covered all 3 agents. Despite all measures, the patient developed refractory shock and died 2 weeks after.

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Severe Varicella Zoster Virus Reactivation After SARS-CoV-2 Vaccination in an Immunocompetent Patient: Case Report

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Contents

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Learning Objectives

- Differential diagnosis and approach to encephalopathy with focal neurological signs.
- Differential diagnosis and approach to acute respiratory insufficiency.
- Differential diagnosis and approach to acute kidney injury.
- Differential diagnosis and approach to a non-bacterial and non-fungal causes of septic shock.
- Diagnosis and management of Intensive Care Unit complications.
- Ethical issues in treatment withdrawal.

10.1 Introduction

Varicella Zoster Virus (VZV) is part of the alpha-herpesvirus family and can establish latency in cells following an episode of primoinfection known as varicella. Clinical reactivation of this virus usually accompanies a period of physical or emotional stress and is more prevalent in elderly and immunosuppressed patients, most often resulting in a painful vesicular eruption localised to one dermatome known as herpes zoster. Disseminated disease, characterised by extension of cutaneous lesions to more than one dermatome or involvement of ophthalmic, splanchnic, cerebral and motor nerves, have been reported in VZV reactivation, and usually indicates immune system dysregulation (1). Pulmonary reactivation is exceedingly uncommon in the absence of profound immunosuppression. The authors describe a case of disseminated varicella zoster reactivation in an 80-year-old man without a recognisable immunosuppressive cause, complicated by multiple organ failure, requiring intensive care support.

Case Presentation

An 80-year-old man presented to the emergency department of another hospital with a two days history of left eye pain and a painful rash in the left upper third of his face. He was diagnosed with ophthalmic zoster, prescribed brivudine and was discharged, returning two hours later due to sudden onset of agitation, confused speech and left-sided hemiparesis that resulted in a fall and head trauma.

He had past medical history of hypertension, chronic obstructive pulmonary disease (Global Initiative for Chronic Obstructive Lung disease—GOLD—stage A) and gout on regular olmesartan/hydrochlorothiazide, nebivolol, amlodipine, alopurinol, furosemide, inhaled fluticasone/salmeterol and glycopyrronium bromide. He had received the third booster dose of SARS-CoV-2 BNT162b2 vaccine 3 days before symptoms onset. He had stopped smoking 6 years before. Nil other history was mentioned.

In the Emergency Department the patient was alert, with a left-sided hemiparesis, dysarthria and neck rigidity. There was a rash involving the dermatome of the ophthalmic branch of the left trigeminal nerve and left eye chemosis. A head computed tomography (CT) with angiographic study revealed a millimetric acute left parafalcine subdural haema-

toma and no other acute traumatic, ischaemic or haemorrhagic lesions. Initial bloodwork showed a C-reactive protein of 4.8 mg/dL and a creatinine of 2 mg/dL. A lumbar puncture revealed elevated cerebrospinal fluid proteins (107 mg/dL, ref. value 15–45 mg/dL) and 6 cells of mononuclear predominance with normal cerebrospinal fluid glucose. A presumptive diagnosis of encephalitis was made, and intravenous (IV) acyclovir was immediately started. He was admitted to the acute medical unit and during the next 24 h the clinical picture deteriorated with the onset of a febrile picture max 39.1 °C, tachypnoea with SpO_2 88–94% on room air. Arterial blood gas showed (ABG) type 1 respiratory failure and the chest x-ray revealed bilateral interstitial infiltrates. The patient was admitted to the infectious diseases ward at our hospital. Further investigations were sought, a chest CT (Fig. 10.1) revealed diffuse bronchial wall thickening, diffuse interstitial peri-hilar infiltrates involving predominantly the upper lobes and apical segments of the lower lobes. The presumptive diagnosis of varicella zoster pneumonia with possible concomitant bacterial infection was made, and in addition to IV acyclovir, he was given 750 U of Human Varicella-Zoster Immunoglobulin and started on amoxicillin/clavulanate and azithromycin. In the following hours, his clinical condition deteriorated further with confused speech and agitation, high lactataemia (39 mg/dL) in the absence of hypotension, oliguria and progression to type 2 respiratory failure (ABG whilst on FiO_2 100%: pH 7.235, pCO_2 52.5 mmHg, pO_2 50 mmHg, HCO_3 19.3 mmol/L), leading to a trial of bi-level non-invasive ventilation. The patient was referred to the

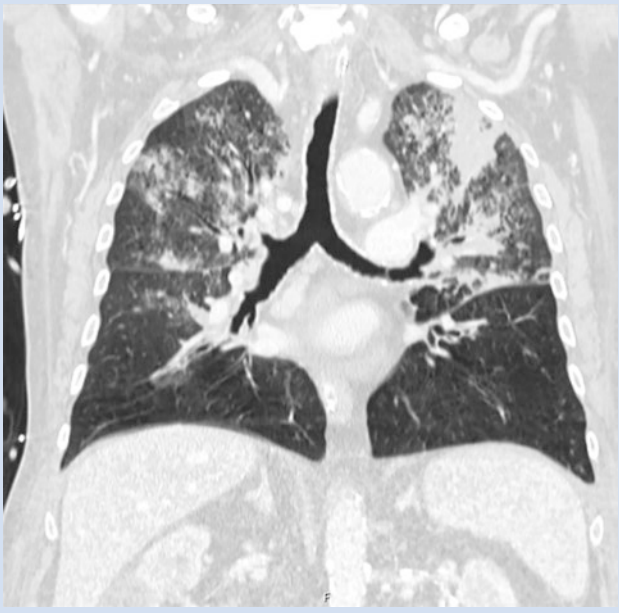

Fig. 10.1 Chest computed tomography scan performed before ICU admission

intensive care medicine team who identified early signs of respiratory exhaustion. He was intubated and mechanically ventilated and transferred to the intensive care unit.

On admission he was sedated targeting Richmond Agitation Sedation Scale (RASS) -5 with isochoric pupils and symmetrical corneal reflexes. He was hypotensive with increased capillary refill time and a peripheral oximetry of 89% under FiO_2 100% on invasive mechanical ventilation. He had a vesicular rash involving the left V1 trigeminal territory, left eye chemosis without keratitis and bilateral lung crackles on auscultation. An ABG revealed a mixed respiratory and metabolic acidaemia. Bloodwork (Table 10.1) confirmed deteriorating kidney function, increasing inflammatory markers, leukocytosis with an absolute lymphopaenia and urinalysis was positive for leukocytes, erythrocytes and proteins. Coagulation and liver parameters were normal. Bedside transthoracic echocardiogram and lung ultrasound excluded obstructive or cardiogenic shock, right ventricular overload and pneumothorax. He was started on noradrenaline and continuous venovenous hsemodiafiltration (CVVHDF) with an effluent dose of 35 mL/kg/h, a fluid removal rate of 100 mL/h without anticoagulation due to subdural haematoma. Oxygenation was compromised with non-protective mechanical ventilation (Table 10.2) so he was proned with an adequate oxygenation response (increase in PaO_2/FiO_2 ratio to 100 under FiO_2 60%). The attending team posed an initial diagnostic hypothesis of septic shock due to bacterial pneumonia, complicated by acute respiratory distress syndrome, meningoencephalitis and acute kidney injury. Previous empiric antibiotic therapy was modified to piperacillin/tazobactam and vancomycin, IV acyclovir was maintained. Several specific diagnostic investigations to confirm both these hypotheses and an immunosuppressive condition were performed in the following days.

Table 10.1 Bloodwork results on ICU admission day 1

	Results	Reference range
Arterial blood gas		
pH	7.18	7.35–7.45
pCO_2	77 mmHg	35–45 mmHg
pO_2	68 mmHg	67–104 mmHg
HCO_3	23 mg/dL	22–30 mmHg
Lactate	19 mg/dL	4.5–14.4 mg/dL
Creatinine	3.32 mg/dL	0.6–1.2 mg/dL
Urea	170 mg/dL	15–43 mg/dL
C-reactive protein	34 mg/dL	< 0.5 mg/dL

Table 10.1 (continued)

	Results	Reference range
Procalcitonin	12 mg/dL	< 0.1 mg/dL
Leukocytes Neutrophyles Lymphocites	15,240x10^9/L 14,290x10^9/L 0,25x10^9/L	3,54–9,06x10^9/L 1,42–6,34x10^9/L 0,71–4,53x10^9/L
Urinalysis		
Leukocytes Erythrocytes Proteins	++ ++ +	– – –

Table 10.2 Ventilation parameters at several timepoints during ICU admission

ICU admission day	**1**	**2**	**4**	**7**	**15**
Ventilatory mode	**Volume-controlled**	**Volume-controlled (prone)**	**Volume-controlled**	**Pressure-support (8 cmH_2O)**	**Volume-controlled**
Tidal volume (mL/kg predicted body weight)	7	6	6	7–8	7
PEEP (cmH_2O)	10	10	10	8	6
Respiratory rate (cycles/min)	28	28	28	20–25	22
Plateau pressure (cmH_2O)	24	22	21	–	25
Driving pressure (cmH_2O)	14	12	11	–	19
Static compliance (mL/cmH_2O)	36	36	38	–	26
FiO_2 (%)	100	40	40	25	40
PaO_2/FiO_2 ratio	74	185	217	303	190

10.2 Investigations

Transthoracic echocardiography (on admission): normal left ventricular size with normal ejection fraction and slight concentric hypertrophy with type 1 diastolic dysfunction with an E/E' of 13 suggestive of normal-high filling pressures; slight right ventricle dilatation with normal longitudinal function and an estimated pulmonary arterial systolic pressure of 40 mmHg.

Flexible Bronchoscopy (on day 3): Diffuse mucosal hyperaemia and oedema involving the trachea, all main and segmental bronchi, with scattered herpetic-like lesions characterised by red papules and vesicles. Clear mucoidal bronchial secretions were aspired and a bronchoalveolar lavage was performed on the right middle bronchus, with a cloudy fluid collected in all syringes.

Head and chest-abdominal-pelvis CT scan with angiographic study (on day 3): reduction in the size of the subdural haematoma, without significant mass effect. Ill-defined densification involving predominantly the central areas in both lungs and in the upper lobes, in some of them with associated small consolidations. There was a small bilateral pleural effusion. No other relevant findings were described.

Electroencephalogram (on day 4, immediately after sedation hold): slow basal electrogenesis activity, ill-differentiated and slightly asymmetrical, without epileptiform or periodic discharges.

Flexible Bronchoscopy (Fig. 10.2) (on day 7): improvement of previous findings, with a subjective reduction in the number and size of the vesicular lesions in the bronchial mucosa.

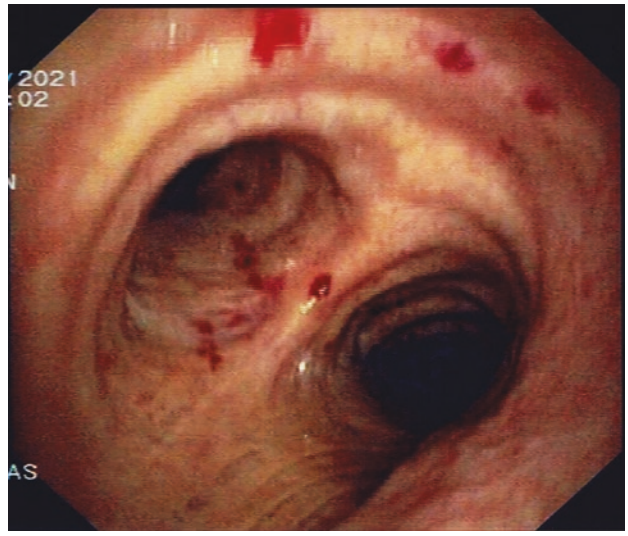

Fig. 10.2 Bronchoscopy performed at day 7 (carina in the image)

Brain magnetic resonance imaging (on day 7): slight hyperintense T2/flair lesions involving the medial temporal, insular and hippocampus bilaterally, compatible with encephalitis. Chronic subdural right frontoparietal and left frontal haematomas with chronicity features and without significant mass effect. Diffuse cortical and subcortical atrophy pattern.

Specific laboratory studies: immunoglobulin levels were normal. Antineutrophil cytoplasmic (proteinase-3 and myeloperoxidase) and anti-glomerular basement membrane antibodies were negative and complement levels were normal. Immunological work-up revealed total lymphopaenia that worsened since admission. No significant alterations were found in major lymphocyte subsets distribution or immunoglobulins production (CD4/CD8 > 1, and normal serum levels of immunoglobulins despite low B cells (1,6%)). No thymoma was observed in Chest CT. Search for plasma autoantibodies against Interferon-γ, Interleukin-17A, Granulocyte macrophage colony-stimulating factor and interleukin-23 were negative in two time points.

Infectious disease screening/ investigation: Polymerase Chain Reaction (PCR) for VZV was positive on blood, cerebrospinal fluid, bronchial secretions, bronchoalveolar lavage and on face vesicles swab. Blood, bronchial secretions, bronchoalveolar lavage, urine and cerebrospinal fluid cultures were negative for aerobic and anaerobic bacteria and fungi. Urinary antigens for pneumococcus and legionella were negative. PCR for other respiratory virus on lower respiratory tract samples and for neurotrophic viruses on cerebrospinal fluid sample were negative. PCR for Human Immunodeficiency Virus 1 and 2 were negative. PCR for *Pneumocystis jirovecci* and *Mycobacterium tuberculosis* on bronchoalveolar lavage were negative.

10.3 Differential Diagnosis

Respiratory failure was an early sign in this patient and appeared 3 days after the rash onset and in the first 24 h of hospital admission. This was associated with fever, bilateral lung infiltrates and elevated inflammatory markers. The most likely attributable causes were viral pneumonia with a possible bacterial superinfection (community or hospital acquired) or other infection associated with an immunosuppressive condition. Pneumonia is a feared complication of acute varicella infection in adult patients, but the fact that only one dermatome was affected by the characteristic vesicular rash indicated a more likely diagnosis of herpes zoster. Therefore, other viral infections and non-infectious causes for acute lung injury were also sought. The patient had risk factors for chronic heart failure, so cardiogenic lung oedema or fluid overload complicating acute kidney injury were investigated. Acute lung injury associated with immunological conditions such as diffuse alveolar haemorrhage or pulmonary-renal syndromes were less probable. Respiratory deterioration preceding ICU admission and motivating urgent endotracheal intubation and ventilation could, therefore, be caused by primary acute respiratory distress syndrome but all other above-mentioned conditions needed exclusion so to confirm this hypothesis.

On ICU admission, the patient was hypotensive with signs of tissue and organ hypoperfusion, so shock approach and haemodynamic evaluation were performed. Previous history suggested septic shock caused by pneumonia, but other concurring conditions could be suspected such as hypovolemia caused by volume depletion, acute heart failure or obstructive shock from pulmonary embolism.

Possible aetiologies for the distributive shock were sepsis caused by bacterial pneumonia. Other infectious non-bacterial organisms were searched. Viral aetiology was considered after cultures for bacterial and fungal organisms were negative and varicella zoster viraemia was confirmed. Organ dysfunctions on ICU admission were precipitated by shock, but they were previously present in the initial clinical picture so other additional causes were considered.

Encephalopathy with focal neurological signs was the initial presentation that motivated hospital admission, and this followed the diagnosis of left V1-trigeminal and ophthalmic zoster, so the most probable cause was varicella encephalitis. The deterioration that preceded ICU admission could be explained by sepsis, uraemia and hypercapnia, but other causes such as subtle status epilepticus and mass effect from subdural haematoma were also considered.

Regarding kidney injury, he had risk factors for chronic kidney disease (age and hypertension), and a previous glomerular filtration rate was not provided so this could not be excluded. Acute kidney injury preceding ICU admission could be attributed to pre-renal causes, namely hypovolaemia secondary to fever and tachypnoea. Renal causes considered were crystal-induced nephropathy complicating IV acyclovir therapy or immunologic phenomena induced by VZV reactivation, namely glomerulonephritis, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis or pulmonary-renal syndromes such as antiglomerular basement membrane disease. Post-renal causes such as renal calculus from previous hyperuricemia history were also possible.

Lastly, varicella-virus reactivation is generally associated with immunosuppressive conditions, but he did not have any as far as it was apparent from previous history. Therefore, acquired immune deficiencies such as human immunodeficiency virus infection, haematological malignancies, or recent SARS-CoV-2 vaccination were the most probable causes. Innate immune defects were less likely, mainly due to his age.

10.4 Treatment

Initial treatment for varicella zoster virus reactivation consisted of IV acyclovir (dose adjusted to CVVHDF and to glomerular filtration rate after CVVHDF interruption on day 6) continued for 21 days due to central nervous system involvement. Empiric antibiotic therapy with piperacillin/tazobactam and vancomycin was interrupted when culture results returned negative.

He was under neuromuscular blockade until day 3, and sedation hold trials were started at day 4. Incomplete consciousness recovery (eye opening to pain stimuli and abnormal flexion response) with purposeless rapid head movements followed sedation hold trials triggered additional investigations (brain CT and electroencephalo-

gram). Epileptic activity and active hydrocephalus caused by possible subdural hematoma expansion were excluded at day 4, so sequelae of encephalitis and possible hyperactive delirium were assumed thereby requiring dexmedetomidine and quetiapine association for patient protection and nonpharmacologic measures such as daily family visits.

He remained on prone ventilation for 17 h (◘ Table 10.2). Ventilation weaning started at day 4. At day 7, he could continuously tolerate pressure support ventilation. Further ventilation weaning and spontaneous breathing trials were not possible due to incomplete neurological recovery and Intensive Care Unit acquired muscle weakness.

Haemodynamic monitoring was performed using conventional haemodynamic parameters, echocardiography and minimally invasive arterial pressure waveform analysis. Initial haemodynamic evaluation was compatible with distributive shock, after exclusion of other aetiologies. Due to increasing dose of noradrenaline that reached 0.75 mcg/kg/min, the patient was started on empiric hydrocortisone 50 mg qid. In the first 24 h, he presented haemodynamic improvement with progressive decrease in the noradrenaline requirements until suspension and achieved complete lactataemia clearance. Hydrocortisone was suspended on day 3. On days 2 and 6, he had episodes of paroxysmal atrial fibrillation without haemodynamic compromise and was successfully submitted to rhythm control with amiodarone. Therapeutic anticoagulation with low-molecular-weight heparin was started after this last episode and after confirming a reduction in the size of his subdural haematoma.

CVVHDF dose was progressively reduced according to metabolic control and fluid removal was adjusted to maintain a neutral/ balanced daily fluid balance. He maintained oliguria until day 5 when spontaneous diuresis of more than 500 mL/day was verified with reasonable uraemia and metabolic control (urea 82 mg/dL), allowing for CVVHDF interruption. Estimated glomerular filtration rate stabilised at 20 ml/min in the following days.

10.5 Evolution, Outcome and Follow-up

Haemodynamic and ventilatory improvements in the first 6 days allowed for spontaneous awakening trial trials, but incomplete consciousness recovery emerged and was characterised by spontaneous eye opening without pursuing the observer, spontaneous non-intentional and non-provoked short amplitude proximal movements of his upper limbs and rhythmic left-right (“no-no”) brisk movements of his head. It was also evident an asymmetric hypotonic quadriparesis with absent osteotendinous reflexes. Repeat head-CT scans excluded any deterioration of previous lesions, and repeat electroencephalograms revealed only slow basal and ill-defined activity without any paroxysmal bursts compatible with epileptic seizures. Initial hypothesis was minimally conscious state due to encephalitis, IV acyclovir toxicity and possible hyperactive delirium. An ICU acquired weakness was also a probable diagnosis. Spontaneous brisk head movements required continuous IV sedation with propofol and dexmedetomidine to avoid self-extubating, thereby prolonging initial ventilation period.

On day 15, the patient worsened with the onset of distributive shock, superimposed acute kidney injury (oliguria and uraemia) and worsening hypoxemia. Ventilator-associated pneumonia diagnosis was confirmed by the identification of a new right inferior lobe consolidation on a CT scan, purulent bronchial secretions and raising inflammatory markers. Cultures were performed, and empiric antibiotic treatment with meropenem and vancomycin was started. A multi-drug resistant *E. coli* with sensitivity to meropenem was isolated on bronchial secretions on day 17, so vancomycin was stopped. He required sedation to target RASS -5 and neuromuscular blockade due to worsening ventilation (Table 10.2), vasopressor support with noradrenaline at a maximal dosage of 1mcg/kg/min, empiric hydrocortisone 50 mg qid and CVVHDF. During the following 48 h, he improved his haemodynamic and ventilatory conditions. At day 17, he stopped vasopressor and attained previous PaO_2/FiO_2 ratio. However, kidney function did not improve to previous level and he remained oliguric and dependent on dialysis for metabolic and fluid balance control.

Ventilatory weaning resumed but on spontaneous awakening trial the previously described neurological syndrome emerged. Another electroencephalogram excluded status epilepticus, uraemia was corrected and no other metabolic disorders were identified. A presumptive diagnosis of nonspecific movement disorder secondary to encephalitis, very similar to Bobble Head Doll syndrome previously described in children with hydrocephalus, was considered. Therapy with clobazam, levetiracetam and valproic acid (doses titrated to 10 mg, 750 mg bid and 500 mg tid, respectively) resulted in brisk head movements control but without consciousness improvement. Percutaneous tracheostomy was then performed at day 21 and at day 30 he had a Full Outline of UnResponsiveness Score (FOURs) of 8 (E3M0B4R1), so active rehabilitation still wasn't possible. He was able to tolerate pressure support-ventilation for only short periods of time, after which increased muscle effort was evident. Diaphragm thickening fraction evaluated at day 38 was 10%, so diaphragm dysfunction probably secondary to prolonged ventilation was confirmed.

Overall condition remained unchanged until day 50. The patient had previously manifested against receiving any measure that could artificially extend his life in the case of an irreversible and severe disabling neurological condition. His case was discussed in a multidisciplinary collegial meeting, and ICU team assumed sequelae of encephalitis preventing him from progressing in rehabilitation and ventilation weaning, associated with persistent kidney failure requiring dialysis. The family was involved to achieve a mutual understanding of patient values and priorities and the role of therapeutic options in achieving patient goals. Life-sustaining treatments were withdrawn, and end-of-life care measures were started. The patient died at day 52.

10.6 Discussion

Sepsis and septic shock are commonly associated with bacterial and fungal infections. Viral sepsis is rare and has been reported in herpes simplex, enterovirus, human parechovirus, influenza, dengue and adenovirus infections in susceptible populations

such as children, pregnant women, immunosuppressed or older individuals (2). Diagnosis of viral sepsis is complex because it requires complete exclusion of bacterial or fungal infection and confirmation of an active viral infection (3). VZV has never been previously reported as a cause of sepsis or septic shock, neither in its acute nor reactivation forms. However, a causal relationship may be established in this case because (1) bacterial, fungal or other viral infections were excluded; (2) VZV was identified by PCR both in affected organs (skin, cerebrospinal fluid and lung) and blood and (3) the patient improved with specific IV acyclovir treatment. This patient presented initially with known complications of VZV reactivation in a dermatome and in the central nervous system, namely ophthalmic zoster and varicella encephalitis. However, he progressed to systemic dissemination with bronchial and lung involvement. All other infectious or immunological conditions were excluded, and bronchoscopy findings associated with a positive PCR for VZV in bronchial secretions and bronchoalveolar lavage support this diagnosis. Pneumonia is the most feared complication of acute VZV infection in adults and has rarely been described in severe immunosuppressed patients with disseminated VZV reactivation (4). In this case, investigation could not demonstrate neither innate nor acquired immunosuppression status. Post-vaccine reactivation of VZV in previously healthy individuals is not unheard of and has most recently been described after SARS-CoV-2 vaccination (5). Although most cases have been mild, a few descriptions of central nervous system involvement have been documented (6). Despite specific treatment that led to an initial improvement, this patient suffered from severe neurological sequelae from encephalitis and several expected complications secondary to prolonged ICU stay and invasive mechanical ventilation, such as ventilator-associated pneumonia complicated by septic shock with irreversible acute kidney injury and ICU-acquired weakness with diaphragm dysfunction. Altogether, these explain the negative outcome of this patient.

This case represents the first account of systemic VZV reactivation with cutaneous, neurologic and pulmonary involvement complicated by distributive shock. It is important to raise awareness of this potential complication so that cases may be rapidly identified and treated like immunosuppressed patients, with intravenous antivirals. Mechanisms involved in VZV reactivation following mRNA vaccines have not yet been elucidated and require urgent investigation.

Take Home Messages

- Varicella zoster virus reactivation may follow SARS-CoV-2 vaccination.
- Disseminated varicella zoster virus reactivation can present as pneumonia and encephalitis in immunocompetent individuals.
- Sepsis and septic shock from viral aetiology is a possibility when all other causes have been excluded.
- Intravenous acyclovir is an effective treatment for disseminated varicella zoster reactivation.

Summary

The authors present the case of a previously immunocompetent 80-year-old patient admitted to the hospital following the onset of an ophthalmic zoster and an acute encephalopathy with focal neurological signs 3 days after SARS-CoV-2 vaccination. Shortly after admission, he developed acute respiratory failure, acute kidney injury and distributive shock and was transferred to Intensive Care Unit (ICU), where he required mechanical ventilation with prone positioning, haemodynamic support and continuous venovenous haemodiafiltration. He was treated with intravenous acyclovir with significant overall clinical improvement in the first 48 h of ICU admission. Haemodynamic failure resolved, dialysis was stopped and oxygenation improved. After extensive investigation, diagnosis of disseminated varicella zoster was confirmed by identification of the virus in blood, cerebrospinal fluid, skin lesions, bronchial secretions and bronchoalveolar lavage. Brain magnetic resonance imaging supported the diagnosis of viral encephalitis. Chest CT scan was compatible with viral pneumonia and bronchoscopy findings suggested mucosal involvement from varicella, both of which were later confirmed by PCR. Bacterial and fungal infections were excluded, as well as has other causes for distributive shock or respiratory insufficiency. Investigation excluded inherited or acquired immunodeficiency. Prolonged ICU stay ensued and was complicated by late ventilator-associated pneumonia, ICU acquired weakness and diaphragm dysfunction. Despite treatment, minimally conscious state persisted and a movement disorder like "bobble head doll syndrome" emerged, presumably as a sequela of encephalitis. Status epilepticus and other structural or metabolic causes were excluded. Further ventilator weaning was not therefore possible, and resuming dialysis was required. Altogether these led to life-sustaining treatments withdrawal after 50 days of ICU stay. Herpes zoster following SARS-CoV-2 vaccination has been previously described, but to the author's knowledge, this is the first report of severe disseminated disease presenting as encephalitis, pneumonia and shock.

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Herpesviridae. A Young Man with Acute Liver Failure and Hemolysis

Vojtech Machek, and Jakub Kletecka

Contents

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Learning Objectives

- Diagnostic approach to an acute liver failure.
- Differential diagnosis of autoimmune hemolytic anemia.
- Treatment of severe autoimmune hemolytic anemia.

11.1 Introduction

We present a rare case of a young man with Epstein Barr virus (EBV) primoinfection, leading to fulminant hepatitis, associated with severe autoimmune hemolytic anemia (AIHA) and multiorgan failure. Although the severity of this disease is uncommon, rapid assessment, focused diagnostics, and the start of proper intensive care and organ support are crucial.

Case Presentation

A 26-year-old man with no relevant medical history visited his general practitioner with one-week-long headaches. In the absence of any other symptoms, only nonsteroid analgesics were prescribed without further examination. A few days later, he developed fevers up to 40 °C and mild pain in the right upper quadrant. The patient presented with these symptoms and mild icterus at the Infectious Disease Clinic. There was no history of traveling, contact with toxins, or hepatotoxic medication. Because of the progression of his condition—decreased level of consciousness and anuric renal failure—he was admitted to our Intensive Care Unit (ICU).

11.2 Investigations

At admission, the clinical investigation showed a patient with drowsiness, hemodynamically stable, with normal capillary refill time, and without any respiratory insufficiency. Fever and mild pain in the right hypochondrium were present. He remained anuric for the first hours, fulfilling acute kidney injury stage 2 according to the Acute Kidney Injury Network (AKIN). Abdominal and head computer tomography showed only hepatosplenomegaly with no other pathologic findings. His lab tests at admission revealed a slight anemia, conjugated hyperbilirubinemia, elevated liver function tests (LFT), urea, creatinine, as well as high procalcitonin and C-reactive protein levels. Hyperferritinemia, unmeasurable high lactate dehydrogenase (LD), and extremely low haptoglobin were found—see Table 11.1. With a working diagnosis of hepatitis and hemolysis, extensive microbiological and autoimmune screening was initiated—results are mentioned in Table 11.2.

Table 11.1 Lab results at ICU admission

Lab results	Value	Lab results	Value
Hemoglobin	67 g/L	Ammoniac	36 µmol/L
Leukocytes	36.2×10^9/L	Creatinine	440 µmol/L
Platelets	187×10^9/L	Urea	26 mmol/L
Bilirubin (conjug.)	305 (205) µkat/L	CRP	47 mg/L
AST	4.6 µkat/L	Procalcitonine	26.1 µg/L
ALT	2.8 µkat/L	Ferritin	24.230 µg/L
GGT	1.9 µkat/L	Ceruloplasmin	0.42 g/L
LD	Unmeasurable high	Haptoglobine	Unmeasurable low

AST aspartateaminotransferase, *ALT* alaninaminotransferase, *GGT* gamaglutamyltransferase, *LD* lactatedehydrogenase, *CRP* C-reactive protein

Table 11.2 Microbiological, virological, and autoimmunity tests, which were performed (positive findings are marked bold)

Micro/virology	Immunology
Leptospira, legionella (antibody)	Antinuclear antibodies
Hepatitis A, B, C, E (PCR/antibody)	Extractable nuclear antibodies
Herpes virus 1,2 (PCR)	Antidouble-strand DNA antibodies
Cytomegalovirus, parvovirus B19 (PCR)	Anti-neutrophil cytoplasmic antibodies
Human immunodeficiency virus (PCR)	Rheumatoid factor
Varicella zoster virus (PCR)	Antismooth muscle antibodies
SARS-CoV-2 (PCR)	Liver kidney microsomes autoantibodies
Parainfluenza, influenza, human herpesvirus 6 (antibody)	Antimitochondrial antibiodies
EBV – Early antibody and viral capsid antigen + PCR	Anti-actin antibodies

11.3 Differential Diagnosis

The most common causes of acute liver failure are infectious (viral), toxic-induced, autoimmune, or metabolic. In addition to the patient's history and course of disease, laboratory tests play a major role in differential diagnosis—polymerase chain reaction (PCR) and antibody testing for hepatotropic viruses and (in Central Europe) uncommon bacterial infections. Toxicologic screening can be done, but the spectrum of toxins is broad and only a few of them can be routinely tested (e.g., acetamino-

phen). Autoimmune screening can reveal the presence of antimicrosomal and smooth-muscle antibodies. Metabolic causes, mainly Wilson's disease, can be excluded with normal ceruloplasmin blood levels and genetic testing (ATP7B gene).

Hemolytic anemia, diagnosed by the decrease of hemoglobin and erythrocyte levels, LD, low haptoglobin, and conjugated hyperbilirubinemia can be primary (inherited, like in sickle cell anemia and thalassemia) or secondary associated with infections, drugs, hematologic malignancy, autoimmune conditions, or as a reaction to a transfusion. The mechanism of erythrocyte lysis involves the production of antibodies against antigens on the erythrocyte wall and the destruction of the erythrocyte intravascularly or in the spleen. According to the type of antibodies, anemias can be divided into AIHA with warm antibodies, cold agglutinin disease (CAD), and paroxysmal night hemoglobinuria (PNH). Direct and indirect Coombs tests, flowcytometry, and focused genetic testing in special cases [1] are the cornerstones of diagnostics.

In our case, the positivity of EBV antigens was found on day 3, confirmed by an extreme load of EBV in plasma—more than 400,000 copies/mL. All other microbiological tests were negative. Hematological tests performed on the first day revealed incomplete warm IgG antibodies. Flowcytometry of the peripheral blood was negative for PNH or malignant lymphocyte clones. Diagnosis of EBV hepatitis and secondary warm AIHA was made.

11.4 Treatment

The patient received standard organ support according to the clinical evolution—one run of continuous renal replacement (indicated on day 2 for lasting anuric renal failure and hyperkalemia), with the use of a polymer absorption filter to control hyperbilirubinemia. A broad-spectrum antibiotic (meropenem) was prescribed until the first negative microbiological test was achieved (discontinued on day 5). There was a need for repeated erythrocyte transfusions on the first days because of rapid hemolysis with hemoglobin falling to 60 g/L. All blood transfusions were given warmed. As there is still no approved antiviral drug for EBV, the off-label use of valaciclovir (1 g three times a day perorally) was discussed and later started due to persistently high EBV loads in plasma. Hemolytic anemia was treated with corticosteroids (prednisone 1 mg/kg) and immunoglobulin (0.5 g/kg a day for 5 days) infusions. Hemolysis was sufficiently controlled on day 5.

11.5 Clinical Evolution, Outcome, and Follow-up

After eight days in the ICU, the patient was transferred in stable conditions to the nephrology ward. His renal function was completely restored after two weeks, and he was discharged from the hospital. LFT fell to normal values in one month. Corticosteroids were tapered without a relapse of hemolysis. The cause of renal failure was diagnosed as a tubulointerstitial lesion of viral etiology. Three months later, the patient returned to work.

11.6 Discussion

Epstein Barr virus is a common herpetic deoxyribonucleic acid (DNA) virus, causing infectious mononucleosis and hairy leukoplakia. Infection is also associated with some hematological malignancies. Primary infection is very common in young people, usually with mild symptoms such as pharyngitis, fever, and lymphadenopathy. More than 90% of the European population has measurable antibodies. In rare cases, severe complications like splenic rupture, meningoencephalitis, hemolytic anemia, or triggered hemophagocytic lymphohistiocytosis are described. In our case, fulminant hemolysis was present. EBV infection with IgG-mediated warm AIHA is uncommon, although well described [2]. Differential diagnosis of AIHA type is critical because of different first-line treatments and exclusion of underlying hematological disease. The etiology of renal failure in our patient was initially unclear, and progression was acute and required renal replacement. Further examination in the nephrology unit was done, but renal biopsy was deferred because of anatomical conditions and restoration of renal functions. The definitive diagnosis of viral-induced tubulointerstitial nephritis was made. The use of polymer absorption is still a controversial therapy but is relatively established in hyperbilirubinemia, caused by hemolysis in this patient. The causal treatment of EBV infection is unavailable at the moment. Nearly all infections are mild and treated symptomatically. Because of persistent high viral loads in plasma PCR controls, an off-label valaciclovir course was initiated, based on case reports and the experience of transplantation nephrologists. This treatment resulted in a rapid decrease in EBV load. No autoimmune disease or underlying hematological conditions were found and the patient was fully immunocompetent.

Take-Home Messages

- Viral hepatitis is one of the most common causes of hepatic failure.
- Autoimmune-mediated hemolysis can be associated with a viral infection.
- Corticosteroid course and immunoglobulin infusion are the first-line treatment for warm AIHA.

Summary

In this case, we present a previously healthy young man with a short history of headaches and fever. He presented with signs of liver and renal failure at admission to the hospital and was transferred to the ICU for the progression of multiorgan failure. From initial exams, a diagnosis of hepatitis and autoimmune hemolytic anemia was made. Broad microbiological and hematological testing was performed. Upon investigation, the cause was determined to be a primary infection with Epstein Barr virus. This infection caused hepatitis and hemolytic anemia. A severe course of hemolysis required repeated transfusions. Continuous renal replacement with polymer absorption was needed because of anuric renal failure and hyperbilirubinemia. After the diagnosis of present warm agglutinins, hemolysis was successfully treated with corticosteroid and immunoglobulin infusions. Upon stabilization, the patient was transferred to a nephrology unit where his renal functions were completely restored. Successful off-label treatment of EBV with valaciclovir was later performed.

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Organizing Pneumonia Treated with High-Dose Methylprednisolone in an Adolescent with COVID-19 Pneumonia Under Extracorporeal Membrane Oxygenation

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Contents

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Learning Objectives

- Not only adults but also children and adolescents suffering from obesity and metabolic disease are at high risk of developing severe COVID-19.
- Organizing pneumonia is a rare complication of acute pulmonary diseases and can be found in adolescents.
- In severe cases of organizing pneumonia, higher doses of glucocorticoids or even cytotoxic agents can be necessary although the treatment remains empirical.

12.1 Introduction

In adult patients, several late effects of coronavirus disease-2019 (COVID-19) are well known such as chronic fatigue, neurologic deficits, or persistent impaction of pulmonary function. Regarding the latter, growing evidence suggests a link between COVID-19 and organizing pneumonia (OP), a rare form of interstitial lung disease (ILD) often caused by viral pneumonia. After initial stabilization, patients with OP present with a secondary deterioration or lack of recovery in pulmonary function without evidence of superinfection or other external causes. Furthermore, the radiological and laboratory findings in OP are diverse and non-specific so it often remains a diagnosis of exclusion. The therapeutic intervention of choice is usually a systemic glucocorticoid therapy. When glucocorticoids fail or are contraindicated only few therapeutic options like azathioprine or mycophenolate mofetil can be considered but lack strong evidence and carry the risk of severe side effects. While there are several case reports and series from adult patients with OP following COVID-19, this clinical picture is not yet described in children or adolescents. In this case report, we want to describe the case of a 16-year-old boy who developed OP secondary to a prolonged severe ARDS with the need of invasive ventilation and extracorporeal membrane oxygenation (ECMO).

Case Presentation

A 16-year-old boy tested positive for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) on the December 23, 2021, developed progressive dyspnea and fever. After 3 days of weakness and loss of olfactory sense, he was admitted to the local primary care center via emergency medicine system. Due to his young age, the patient was directly transferred to the pediatric Intensive Care Unit (ICU) of a university hospital. Upon admission, the patient presented with a moderate ARDS and tachypnea (30 min). Under high-flow oxygen therapy (HFNC), arterial parteial pressure of oxygen (P_aO_2) was 64 mmHg with 0.8 fraction of inspired oxygen (FIO_2). Beside class II obesity (169 cm height, 104 kg BW, BMI 36 kg/m^2), no comorbidities or allergies were reported. The patient lived with his parents, who tested positive for SARS CoV-2 shortly after him and had not been vaccinated by that time. Laboratory analysis revealed elevated concentrations of C-reactive protein (94.8 mg/L) and procalcitonin (0.51 ng/L) but no elevated leukocytes (5.46 GPt/L) or lactate (1.0 mmol/L).

12.2 Investigations

On the day of admission, chest X-ray showed bilateral pulmonary infiltration. Due to the high severity of illness a computed tomography (CT) scan with pulmonary angiography was performed, which showed ground-glass opacities typical for COVID-19 pneumonia and ruled out pulmonary embolism (Fig. 12.1). SARS CoV-2 infection was confirmed via polymerase chain reaction (PCR) that revealed the delta variant (B.1.617.2) with a cycle threshold of 22.6. There were detectable immunoglobulin-G (IgG)-antibodies to S- and N-proteins at low concentrations. Due to the elevated inflammatory parameters, blood cultures were drawn that ruled out blood-stream infection, and oropharyngeal swab for multiresistant pathogen testing was performed which showed colonization with methicillin-sensitive *Staphylococcus aureus* (MSSA). When his condition worsened, repeated bronchoscopy was performed with bronchoalveolar lavage and negative testing for atypical pathogens like *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Aspergillus, Legionella pneumoniae, Herpes viridae, or pneumocystis* spp. Other causes of ARDS like vasculitis or drug toxicity were ruled out.

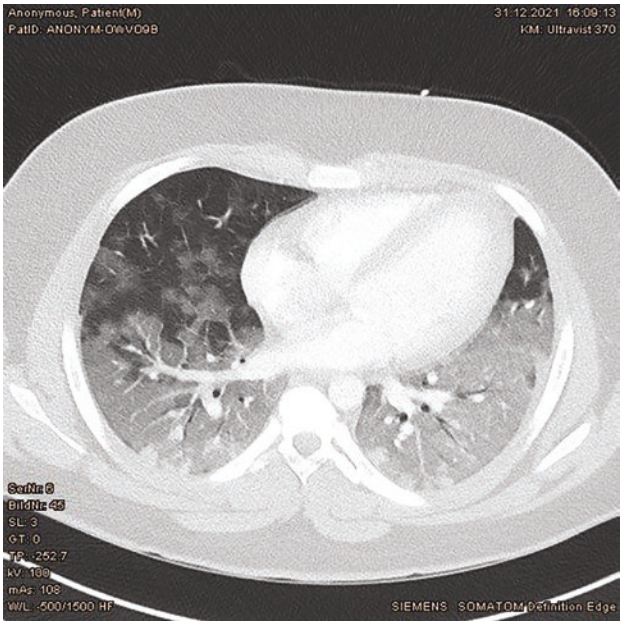

Fig. 12.1 Computed tomography scan on admission showing dorso-basal ground-glass opacities

12.3 Differential Diagnosis

The patient presented himself with symptoms of acute pneumonia and a confirmed COVID-19 infection. Because of the rarity of severe COVID-19 infections in children and adolescent, differential diagnoses that come along with dyspnea and fever such as bacterial pneumonia, pulmonary embolism, and sepsis were ruled out.

12.4 Treatment

According to current guidelines, the patient received a COVID-19-specific therapy with systemic dexamethasone (6 mg i.v.) for ten days and a single dose of tocilizumab (1 × 800 mg i.v.) on day of admission. After initiation of ECMO on day 16 and confirmed progression of bilateral pulmonary ground-glass opacities (Fig. 12.2), a calculated antibiotic therapy with piperacillin/tazobactam and clindamycin was started. In the absence of improvement and without evidence of pulmonary superinfection, a first systemic glucocorticoid therapy was initiated on day 22 with 2 mg prednisolone per kg BW for 3 days and tapered over the next weeks which did not led to a sustainable improvement. In view of the progressive dorso-basal consolidations and persistence of respiratory failure, intermittent prone positioning was continued 27 times in total.

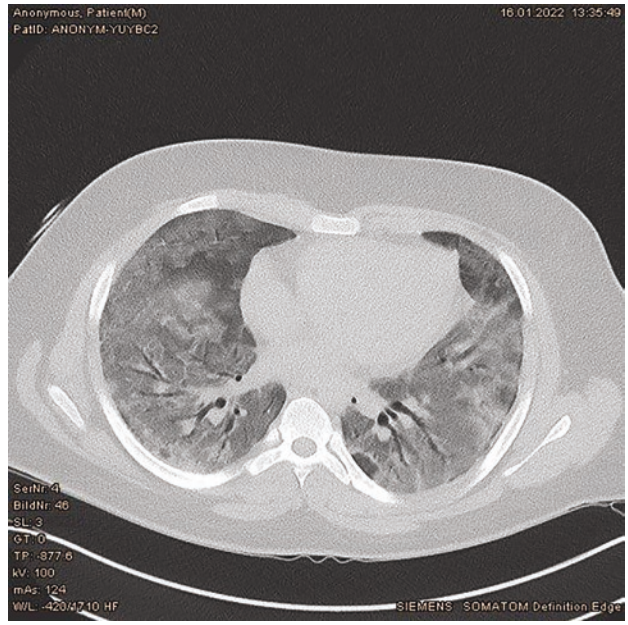

Fig. 12.2 Computed tomography scan on day 16 showing progressive opacities and beginning consolidations

12.5 Evolution, Outcome, and Follow-up

Subsequently, the respiratory situation stabilized, but the patient was still ECMO-dependent. A repeated CT scan on day 46 showed new bilateral pulmonary reticulations and overall migrated opacities (Fig. 12.3). At this point, OP was not considered because the patient was already under systemic glucocorticoid therapy. After reduction of sedation, the patient showed severe tachypnea and strong patient-ventilator asynchronies, thus he was put on neurally adjusted ventilatory assist (NAVA)-ventilation from day 63. At the same time, a further progression in bilateral pulmonary opacities was shown via chest X-ray. Under NAVA-ventilation, ECMO therapy could be reduced but further weaning was not possible. Under the assumption of an ongoing or relapsing OP, a new high-dose glucocorticoid therapy with methylprednisolone 10 mg/kg BW for 3 days was started on day 80. Hereafter, ECMO therapy could quickly be reduced and functionally terminated by day 84. After removal of the ECMO cannulas on day 88, weaning and mobilization improved substantially. To prevent reinfection, the patient received the first dose of COVID vaccination on day 94 while still on ICU. At point of discharge to rehabilitation on day 110, the patient was awake and showed no signs of central neurologic deficit. He was weaned to speaking valve through the day but required ventilator support at night.

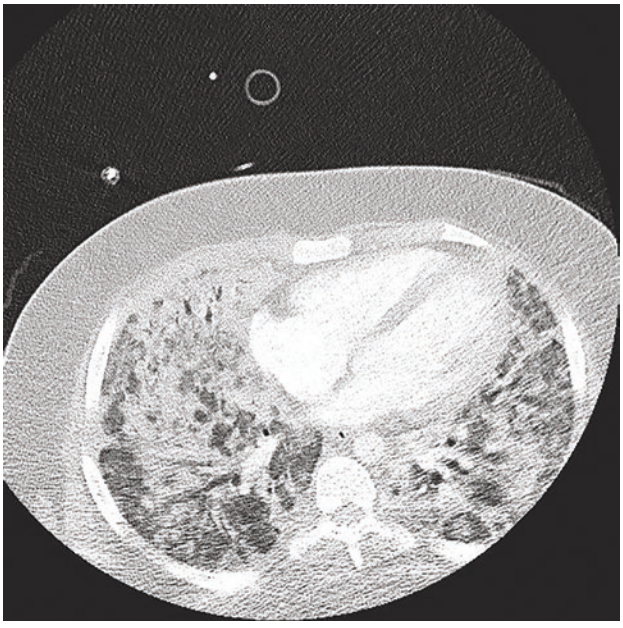

Fig. 12.3 Computed tomography scan on day 46 showing severe consolidations with signs of fibrosis and persistent inflammation

12.6 Discussion

To our knowledge, this is the first report of refractory OP with prolonged severe pulmonary failure in an adolescent with COVID-19. Several aspects on this case are worth mentioning. First, while well known in adults, severe ARDS due to COVID-19 is scarce in children and adolescent and requirement for ECMO is even more rare. Only 42 (0.4%) of 10,245 hospitalized children with COVID-19 received ECMO therapy [1]. All of the few reported cases on ECMO therapy in children or adolescents with COVID-19 showed a quick recovery with median time on ECMO of 11 days, while in the reported case ECMO-time was 72 days [2]. Second, previous studies of severe COVID-19 in children often described patients with preexisting severe comorbidities such as malignancies, developmental, or genetic anomalies [3]. A current study now shows that young- and middle-aged adults (18–55 years) with obesity and metabolic disease (diabetes, arterial hypertension) suffer the same risk of mortality due to COVID-19 as older adults (56–75 years) [4]. In a recent analysis of 947 children hospitalized with SARS-CoV-2, obesity increased the probability of severe illness by factor 2.20–2.48 [5]. Third, organizing pneumonia as a response to a specific lung injury is an emerging complication in COVID-19. While pathogenesis of OP is poorly defined, an inflammatory and fibroproliferative process of the lung tissue with intra-alveolar buds (Masson's bodies), fibrosis, and remodeling is assumed to be the main pathogenic mechanism [6]. This process usually becomes clinically visible after the acute phase of the underlying illness but varies widely both in symptoms and radiological findings. OP has to be considered in any patient with overcome pneumonia who shows symptoms of new pulmonary deterioration and/or progressive radiological signs of pulmonary consolidations or opacities which cannot be associated with another cause like superinfection or else [6]. Most cases of OP are well responsive to moderate-dose glucocorticoid therapy (e.g., 1–2 mg/kg BW Prednisolone for 5–10 days). In the present case, moderate-dose prednisolone was started with the ECMO therapy after exclusion of other causes of secondary deterioration as mentioned above, while the CT-scan showed progressive opacities and mediastinal lymphadenopathy but failed to show improvement. In the further course with recurrence of radiologic impairments and persistence of lung failure, a new, high-dose, glucocorticoid therapy was initiated (10 mg/kg BW methylprednisolone over 3 days), under which the clinical condition improved remarkably within days. The used dosage in this case is much higher than published therapeutic plans for OP, yet it is known that for some cases of OP the published doses are not sufficient [6]. In summary, based on the reported case, OP should be considered even in young patients with relapsing or persisting lung failure if no other cause can be identified. After careful consideration high-dose glucocorticoids can be effective in severe cases.

Take-Home Messages

- Not only adults but also children and adolescents suffering from obesity are at high risk of developing severe COVID-19.
- Organizing pneumonia is a rare complication of acute pulmonary diseases and can be found in adolescents.
- In severe cases of organizing pneumonia, higher doses of glucocorticoids can be necessary, although this treatment remains empirical.

Summary

A 16-year-old boy was transferred to our pediatric Intensive Care Unit (ICU) with moderate acute respiratory distress syndrome (ARDS) due to COVID-19 pneumonia. He had tested positive for severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) three days prior to admission and since experienced progressive dyspnea, weakness, and fever. There were no comorbidities besides class II obesity (BMI 36 kg/m^2). Furthermore, he was unvaccinated against SARS-CoV-2. He received dexamethasone, tocilizumab, and noninvasive respiratory support via high-flow oxygen therapy (HFNC), noninvasive positive pressure ventilation (NIV), and awake prone positioning. After 16 days, he progressed to severe ARDS and had to be intubated and put on venous-venous extracorporeal membrane oxygenation (ECMO) due to refractory hypoxemia. Because of radiological appearance of progressive bilateral pulmonary basal consolidation, cryptogenic organizing pneumonia was suspected. In addition to continuing prone positioning under ECMO therapy, a systemic glucocorticoid therapy with 2 mg/kg BW prednisolone over 3 days was initiated but failed to improve pulmonary function sustainably. In anticipation of a long-term respiratory support, tracheostomy was performed on day 21. Subsequently, the patient showed excessive patient-ventilator-asynchronies and was put on neutrally adjusted ventilatory assist ventilation (NAVA) on day 63. Despite continuation of a glucocorticoid therapy, bilateral pulmonary consolidations progressed, and new cystic conversions of lung tissue appeared on computed tomography (CT) scans with persisting respiratory failure. Therefore, on day 80, a high-dose methylprednisolone therapy of 10 mg/kg BW was initiated under which respiratory function rapidly improved and ECMO therapy could be stopped on day 84. With further improvement, he received the first vaccination against SARS CoV-2 on day 94 while still on ICU. On day 110, after 72 days on ECMO support, the patient was successfully discharged to rehabilitation without neurological deficit. To our knowledge, this is the first report of refractory organizing pneumonia with prolonged severe pulmonary failure in an adolescent with COVID-19 under ECMO therapy treated with high-dose glucocorticoid therapy.

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Severe Fungal and Parasitic Infections in the Intensive Care Unit

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Contents

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Learning Objectives

- Recognize the relevance of fungal and parasitic infections in the Intensive Care Unit.
- Describe the risk factors and be aware of the difficulty of diagnosing a *Candida* infection in a critically ill patient.
- Understand the epidemiology of the different species of *Candida* and their impact on the treatment. Know the recommended first-line treatment and the de-escalation options.
- Describe the comorbidities and medical background associated with the risk of mucormycosis. Know the clinical presentation and different usual location/sources of infection.
- Summarize the diagnostic tools that can be used to identify mucormycosis and describe the first-line treatments.
- Outline the basic epidemiology, clinical presentation, and diagnosis of malaria.
- Describe the importance of identifying severe malaria and recognize the relevance of initiating therapy immediately.
- Summarize the main presentations of echinococcal disease and the diagnostic and therapeutic approach.

13.1 Introduction

The recent advances in intensive care medicine have contributed to longer survival of the patients, which has led to an increasing incidence of opportunistic infectious diseases caused by fungi. Invasive fungal infections are becoming a problem in the critical care setting because of its associated morbidity and mortality. While most of the infections are due to *Candida* species, other rare pathogenic fungi are emerging, including the order Mucorales or *Aspergillus* species. Early diagnosis and treatment of these infections are essential to improve the outcomes. In this chapter, we will address two representative fungal infections in the Intensive Care Unit (ICU): candidemia/invasive candidiasis and mucormycosis.

Although parasitic infections are uncommon in the ICUs of the developed world, the increase in air travel and tourism and the recent changes in the pattern of migratory movements have led to an increased exposure of individuals to these infectious agents. Thus, thinking of these diseases can be life saving. Suspecting malaria may not be straightforward; however, the treatment of severe malaria is a medical emergency. Other parasitic infections, such as echinococcal disease, can evolve to multiple organ failure and require a multidisciplinary management, where supportive therapy in the ICU may have a central role. In this chapter, we will focus on two relevant parasitic infections in the ICU: malaria and echinococcal disease.

13.2 Candidemia and Invasive Candidiasis

Invasive candidiasis is the most common severe fungal infection in the ICU, affecting up to 5% of all ICU admissions [1]. It affects a wide range of patients, from the immunocompromised ones to patients undergoing prolonged organ support techniques with the use of invasive devices or prolonged antibiotic treatment.

Detection of candidemia is the most common mode of entry into the disease, but diagnosis of invasive candidiasis remains often delayed. Therefore, probability scores to guide diagnosis have been developed to ensure early diagnosis and early empirical treatment.

13.2.1 Epidemiology and Microbiology

Invasive candidiasis remains a healthcare-associated infection, ranging from 80% of healthcare-associated cases to 95% of cases during the COVID-19 pandemic [2]. Among COVID-19 pandemic patients, 80% of invasive candidiasis were acquired in an ICU setting [3]. The minor fraction of non-healthcare-associated candidiasis is mostly related to injection drug use [3].

There are predominantly 5 species responsible for invasive candidiasis in the ICU: *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei*. The most prevalent isolate remains *C. albicans*; however, in a growing number of reports, its prevalence is decreasing in favor of other species, especially *C. glabrata* [3, 4] and *C. parapsilosis* [5]. A nationwide epidemiological study investigating *Candida* blood isolates from hospitalized patients over 15 years (2004–2018) in Switzerland reported a decrease in *C. albicans* isolates rates from 60% to 53% and an increase in *C. glabrata* isolates from 18% to 27% ($p < 0.0001$) [4]. The recent COVID-19 pandemic was associated with an increase in the incidence of invasive candidiasis, and the same trend of high rates of non-albicans species was observed. Recently, a new isolate, *Candida auris* has emerged [1, 5], and its spread has been enhanced by the COVID-19 pandemic. *C. auris* is a nosocomial pathogen that represents a threat to ICUs due to its persistence in the environment and its highly resistant profile, with > 90% of strains being resistant to fluconazole, 35% to amphotericin B, and over 40% expressing combined resistance to two or more classes of antifungals [6].

13.2.2 Diagnosis and Diseases Caused

Candidemia and intra-abdominal infections are the most common sources responsible for invasive *Candida* infection in the ICU as implanted medical devices such as catheters and the gastrointestinal tract are prompt to be colonized by *Candida* biofilms [7].

There are no specific signs of invasive candidiasis, persistent fever despite adequate antibiotic treatment (and no other cause for hyperthermia) being the most common clinical presentation [8]. This persistent fever in critically ill patients should trigger the assessment for *Candida* infection risk factors and culture data from non-sterile sites [9].

A meta-analysis of 34 studies reported five risk factors that were associated with invasive *Candida* infection: broad-spectrum antibiotics administration, blood transfusion, *Candida* colonization, central venous catheter, and total parenteral nutrition [7].

13.2.3 Treatment and Prognosis

In critically ill patients, the administration of an echinocandin is recommended as an initial treatment, then de-escalation to azoles when tested susceptible is possible if the clinical situation has improved [9]. The usual pattern of susceptibility to antifungal agents is presented in ◘ Table 13.1.

Mortality rates associated with candidemia are significant as they were reported to be higher than those of Gram-positive and Gram-negative bacteremia (43% *vs* 25% and 29%, respectively) [8].

Table 13.1 Usual pattern of susceptibility to antifungal agents

Candida species/antifungal agents	Fluconazole	Isavuconazole	Itraconazole	Posaconazole	Voriconazole	Caspofungin	Amphotericin B
Albicans, parapsilosis, tropicalis	+	+	+	+	+	+	+
Glabrata	Variable (higher dose needed if tested susceptible)	Variable	–	Variable	Variable	+	Variable
Krusei	–	+	–	+	+	+	Variable

13.3 Mucormycosis

Mucormycosis refers to an infection caused by fungi of the order Mucorales. The most frequently reported responsible pathogens are *Rhizopus* spp., *Mucor* spp., and *Lichtheimia* spp. [10].

Mucormycosis affects primarily immunocompromised patients. Diabetes was known as the most common risk factor during the twentieth century and, subsequently, further risk factors have been described such as solid organ and hematopoietic stem-cell transplantations, hematological diseases, chemotherapy, and immunotherapy. Traumatic injury, surgery, and burns have also been reported as risk factors for cutaneous and soft-tissue mucormycosis. Most recently, there has been a resurgence of respiratory mucormycosis with the COVID-19 pandemic precipitating an epidemic of mucormycosis worldwide, whereby severe COVID-19 itself has become a risk factor for mucormycosis [11].

Mucormycosis infection involves the Intensive Care Unit (ICU) physician because of the often rapidly progressive and destructive nature of the infection that can lead to sepsis, septic shock, or any isolated organ failure. It requires urgent and rapid diagnosis and intervention, as any delay in initiating treatment is associated with an increased mortality.

13.3.1 Clinical Manifestations

There are four main locations of mucormycosis: pulmonary, cutaneous and soft-tissue, rhino-orbito-cerebral, and gastrointestinal.

Pulmonary mucormycosis is seen in patients with profound neutropenia and in COVID-19 patients. It occurs through inhalation of sporangiospores and is reported in both developed and developing countries. Its diagnosis remains elusive as most of the clinical signs are those of pneumonia (fever, cough, and hypoxemia) and can be easily confused with viral or bacterial pneumonia. Furthermore, imaging findings remain unspecific. In light of these difficulties, experts met during the COVID-19 epidemic to determine the best definitions, diagnostic tools, and recommended management of COVID-19-associated pulmonary mucormycosis [11].

Rhino-orbital mucormycosis is associated with lower mortality than the pulmonary one. Diabetes is the strongest risk factor for rhino-orbital mucormycosis, particularly in patients with poor glycemic control and repeated ketoacidosis. Ketoacidosis leads to higher levels of circulating iron and ferritin. These two elements promote fungi growth. Rhino-orbital mucormycosis was also the most common manifestation in COVID-19 [12].

Cutaneous and soft-tissue mucormycosis are usually defined as the forms of mucormycosis of immunocompetent patients. It usually occurs in patients who suffered traumatic injuries or extensive burns. It has been reported that the state of inflammation associated with these pathologies can classify the patients as immunocompromised as well [13].

Finally, gastrointestinal mucormycosis is an uncommon manifestation in adult patients, as it is rather seen in neonates.

13.3.2 Diagnosis

The diagnosis relies on imaging techniques and laboratory findings (pathological anatomy, culture, and molecular techniques).

- Imaging. For each affected location, guidelines recommend the realization of a computed tomography (CT) scan. In case of suspected pulmonary mucormycosis, a chest CT scan should be performed to identify suggestive radiographical signs. The following features on CT scan were identified as highly suggestive of pulmonary mucormycosis: the presence of a thick-walled cavity, reversed halo sign, large consolidation or necrotizing pneumonia, mycotic aneurysm, bird's nest sign, multiple large nodules, serial imaging showing cavity with an air-fluid level [2].
- Pathological anatomy. In addition, fresh tissue and biopsies should be obtained from the affected location (nasal endoscopy and bronchoscopy are encouraged) for histopathology analysis. To confirm the infection, hyphae must be observed in the tissue.
- Culture. Culture of specimens is strongly recommended for identification and antifungal susceptibility testing.
- Molecular techniques. Finally, the use of molecular techniques still needs to be backed up with high-quality studies and strong evidence but seems promising. Serum PCR has been reported as having high sensitivity and specificity (respectively, 85.2% and 89.8%) for the detection of circulating DNA [14].

13.3.3 Treatment and Prognosis

The treatment of mucormycosis associates surgical techniques and antifungal agents. On the surgical point of view, extensive resection and debridement are recommended whenever possible. This treatment should be repeated as many times as required to ensure complete resection.

In case of suspicion of mucormycosis, regardless of the location, the initiation of the antifungal treatment is absolutely necessity. The diagnostic investigations must not delay the initiation of the antifungal agents. Liposomal amphotericin B is recommended as a first-line agent and is usually used as a monotherapy. Second-line agents are azoles such as isavuconazole and posaconazole. There is no recommendation for a combination therapy except for salvage treatment in case of refractory mucormycosis or toxicity of first-line agents.

13.3.4 Outcomes

This disease is burdened with high mortality rates ranging from 40% to 80% according to the location of the infection, its invasiveness, and the underlying comorbidities of the patient. The cerebral location is the one associated with the highest rates of mortality. Sinus and cutaneous diseases are associated with lower mortality rates probably because their diagnosis is easier and the lesions more accessible to surgical debridement.

13.4 Malaria

Malaria is a life-threatening mosquito-borne infectious disease caused by one or more of the species of the *Plasmodium* genus, transmitted by the bites of infected female *Anopheles* spp. mosquitoes. Up to five species of Plasmodium have been described to cause disease in humans: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae,* and *P. knowlesi* [15]. The most commonly identified species is *P. falciparum*, accounting for 3 out of 4 cases among infected patients, followed from afar by *P. vivax*, which represents 1 out of 5 infections.

13.4.1 Epidemiology

Malaria is an endemic disease, with sporadic cases in travelers returning from endemic areas. It is important to note that, in 2020, 29 of the 85 countries where malaria is endemic accounted for 96% of malaria cases and deaths worldwide [16]. More than half of these cases were concentrated in Nigeria, the Democratic Republic of the Congo, Uganda, Mozambique, Angola, and Burkina Faso. The World Health Organization (WHO) estimated 241 million cases and 627,000 malaria deaths around the globe in 2020 [16]. The estimated mortality rate was 15 deaths per 100,000 population at risk. Most deaths occur in African children <5 years of age [16].

13.4.2 Microbiology

Plasmodium is a genus of unicellular eukaryotes that are obligate parasites of vertebrates and insects. In a simplified way, during a blood meal, infected female *Anopheles* spp. mosquitoes inject the infective, motile stage of the *Plasmodium*, named sporozoites, along with anticoagulant substances. Within 1 h, sporozoites travel into the liver cells, where they undergo a multiple asexual fission process (schizogony), resulting in the generation of thousands of merozoites. These merozoites are released into the bloodstream after the rupture of the hepatocytes, where they invade the red blood cells to replicate (erythrocytic schizogony), causing the symptomatic stage of the disease, which normally occurs within 4–8 days after the initial red blood cells invasion. Some merozoites differentiate into male and female gametocytes, which represent the *Plasmodium* spp. stage that infects the mosquito host when it takes a blood meal. The replication cycle of the merozoites takes 48–72 h, after which red blood cells are lysed, producing a massive release of endotoxins (a complex of hemozoin and parasite DNA, which triggers the activation of the Toll-like receptor 9, leading to the release of TNF-α). This is the reason why fever occurs every 48–72 h (tertian and quartan fever) in patients with infections originated from a single bite (synchronous infection). Merozoites released in this process can invade further red blood cells, increasing the replication rate. *P. vivax* and *P. ovale* can also have a dormant state in the liver, named hynozoites, which may reappear some years after the initial infection, leading to relapse. Gametocytes tend to accumulate in the skin capillaries, where they can be easily taken up by the female *Anopheles* spp. mosquito in a blood meal. In the gut of the mosquito, male and female gametocytes fuse (sexual reproduction process), forming a zygote, which evolves into an ookinete. The ookinete gets outside

the gut of the mosquito across the epithelium as an oocyst. Oocysts experience further replication and form sporozoites, the stage of *Plasmodium* that travels from the abdomen to the salivary glands of the mosquito, where it is ready to infect a new human host [15, 17].

13.4.3 Clinical Presentation

The most common clinical picture consists of flu-like symptoms, including low-degree fever, shaking chills, headache, myalgia/arthralgia, weakness, and digestive symptoms (particularly in children). The symptoms normally present in paroxysms (related to hemolysis of the red blood cells infected by *Plasmodium*) and slowly evolve to high fever, profuse sweating, and asthenia. There is no combination of signs or symptoms that reliably distinguishes malaria from other causes of fever [18].

13.4.4 Diagnosis and Risk Stratification

According to the WHO, the diagnosis of malaria requires the presence of fever and the identification of parasites [19]. Parasitological diagnosis should be available within a short time of the presentation of the patient and can be performed by light microscopic examination of a blood smear or a rapid diagnostic test (RDT). Light microscopy is considered the reference test due to its high sensitivity and specificity and its ability to quantify malaria parasites and the infecting species. Rapid diagnostic tests can be based on the detection of histidine-rich protein 2 (HRP2) (specific for *P. falciparum*), pan-specific or species-specific *Plasmodium* lactate dehydrogenase (pLDH), or pan-specific aldolase [17–19].

Malaria is commonly classified as asymptomatic, uncomplicated or severe. Uncomplicated malaria is defined as the presence of symptoms of malaria, with a positive parasitological test, but with no criteria of severe malaria. Severe malaria is defined as acute malaria with signs of organ dysfunction or high levels of parasitemia (≥500,000/μL or ≥10%). Severe malaria is often fatal, with mortalities of 10% and 20% in children and adults, respectively [15, 19]. Although *P. falciparum* accounts for most cases of severe malaria, *P. vivax* and *P. knowlesi* are also responsible for a relevant fraction of cases. Severe malaria is characterized by severe anemia (due to hemolysis) and organ damage (due to microvascular obstruction of the parasites in the capillaries). The WHO definitions for severe malaria are depicted in ► Chap. 14.

13.4.5 Treatment and Prognosis

The treatment of a patient with malaria should take into account four relevant factors: (1) the infecting *Plasmodium* species; (2) the clinical status of the patient (uncomplicated *vs* severe malaria); (3) the expected drug susceptibility of the *Plasmodium*, according to the geographic area where the infection was acquired; and (4) previous use of antimalarials (including those prescribed as chemoprophylaxis) [17].

The aims of the treatment in patients with uncomplicated malaria are to cure the infection (i.e., to eliminate of all parasites from the body) as soon as possible and to

prevent worsening to severe disease. From a public health perspective, the aims of therapy include the prevention of further transmission and prevention of the development and spread of antimalarial resistance.

The WHO recommends an artemisinin-based combination therapy (ACT) for uncomplicated *P. falciparum* malaria (except for pregnant women in their first trimester) [19]. Administration of a 3-day course of an artemisinin derivative prevents the development of resistance. The WHO-approved first-line ACT options are artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, dihydroartemisinin + piperaquine and artesunate + sulfadoxine-pyrimethamine. The treatment for pregnant women with uncomplicated *P. falciparum* malaria during the first trimester consists of a 7-day course of quinine + clindamycin.

Uncomplicated malaria caused by *P. vivax*, *P. ovale*, *P. malariae,* or *P. knowlesi* can be treated with chloroquine, if chloroquine-susceptible, or ACT (except for pregnant women in their first trimester) [19]. The treatment of choice for pregnant women with uncomplicated chloroquine-resistant *P. vivax* malaria during the first trimester is quinine. To prevent relapse (i.e., to eliminate hypnozoites from the liver), patients with *P. vivax* or *P. ovale* malaria should receive a 14-day course of primaquine in all transmission settings.

The treatment of severe malaria is a medical emergency [19]. All the patients with suspected or confirmed diagnosis should receive intravenous or intramuscular artesunate for at least 24 h (3 doses of 2.4 mg/kg, given at 0, 12 and 24 h). If artesunate is not available, interim treatment with a rapid-onset oral ACT (e.g., artemether + lumefantrine) should be considered while obtaining the first-line therapy. It is recommended to perform a set of thick and thin blood smears every 12–24 h, until *Plasmodium* parasites are not detected. If parasite density persists above 1% after the third dose of artesunate, treatment should be continued at the same dose once a day until parasite density is ≤1%, for a maximum of 6 additional days. Provided that the patient has received at least three doses of artesunate, the parasite density is ≤1% (assessed on a blood smear collected 4 h after the last dose) and the patient can tolerate oral therapy, a full ACT course or an alternative regimen (in particular cases) must be administered.

13.5 Echinococcal Disease

Echinococcal disease or echinococcosis is a parasitic infection caused by the genus *Echinococcus*, which belongs to the class *Cestoda*. Four species of Echinococcus cause disease in humans: *E. granulosus*, *E. multilocularis*, *E. vogeli,* and *E. oligarthrus*. The first two species are the most relevant, which are responsible for cystic echinococcosis (unilocular) and alveolar echinococcosis (multivesicular), respectively. The last two species cause polycystic echinococcosis and are less frequent [20, 21].

13.5.1 Microbiology

The anatomy of *Echinococcus* consists of three basic structures: 1) a scolex or grasping head, adapted to attach to its definitive host (called protoscolex in the larval

stage); 2) a short neck, and 3) a strobila, which consists of several proglottids and forms the body of the worm [20].

The adult stage of *Echinococcus* lives in the small bowel of definitive hosts, which include dogs, wolves, foxes, and lions. Infected definitive hosts shed embryonated eggs in their feces, which contaminate the ground, where they may stay viable for up to one year. These eggs are ingested by an intermediate host (e.g., sheep, cattle, goats, pigs or small rodents) and travel to their small bowel, where they release an oncosphere that penetrates across the intestinal wall and migrates through the circulation into target organs, particularly the liver and the lungs, where it grows and becomes a cyst. The cyst grows progressively, producing protoscolices and daughter cysts inside the cyst. The definitive host gets infected through the ingestion of the cyst-containing organs of the infected intermediate host. After this, the protoscolices evaginate and adhere to the small bowel mucosa of the definitive host, where they evolve to the adult stage (scolex) [20, 22].

Humans are accidental dead-end hosts, since their bodies are seldom eaten by definitive hosts nowadays. The most frequent route of transmission to humans is accidental ingestion of food, water, or soil contaminated by fecal matter of an infected definitive host. This is common in people rising, working, or living with animals that are intermediate hosts.

13.5.2 Cystic Echinococcosis

The infection caused by the larval stage of *Echinococcus granulosus* is called cystic echinococcosis (CE) or hydatidosis. It affects up to 6% of the population in endemic areas, which include Africa, Europe, Asia, Central and South America, and occasionally, North America. The main risk factors are sheep slaughtering in areas close to human and dog settlements and poor hygiene.

Although *E. granulosus* may originate cysts in virtually any organ, most patients exhibit liver (50–70%) or lung (20–30%) involvement. Most patients remain asymptomatic for years or decades, while the cyst grows slowly. Symptoms usually develop in the setting of mass effect due to the increase in the size of the cyst in a limited space. If the cyst invades the biliary tree or a bronchus, it may cause an obstruction, which can present with abdominal or respiratory symptoms, and this in turn may lead to bacterial superinfection or abscess. Two uncommon (<10%) but severe complications may arise in these patients: (1) cyst rupture, which may cause fever, hypotension, and anaphylaxis due to the release of antigenic material from the parasite, and (2) secondary spread of the infection by daughter cysts with involvement of multiple organs, which may lead to multiple organ failure [23].

Hydatidosis is usually diagnosed by imaging techniques in conjunction with serology. Cysts are frequently diagnosed in patients undergoing imaging techniques for other reasons. Imaging techniques show a great sensitivity (>90%) and include ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). Serologic status of the patient may be tested by ELISA or Western blot. While serologic diagnosis yields a high sensitivity and specificity for patients

with liver involvement (>80%), the diagnostic performance declines in other locations (<50%). For this reason, a negative serology cannot rule out the diagnosis [20].

There is no optimal evidence-based therapeutic approach for cystic echinococcosis. The WHO has developed an ultrasound-based classification system for the disease, which is useful for guiding general management [24]. The therapeutic approach may range from observation (in patients who remain asymptomatic or who present with inactive stages) to interventional strategies (including surgery and Puncture, Aspiration, Injection, and Reaspiration [PAIR]) and usually includes the use of anthelminthics (albendazole) [20, 22].

13.5.3 Alveolar Echinococcosis

The infection caused by *Echinococcus multilocularis* is called alveolar echinococcosis (AE). Although less frequent than CE, AE is normally symptomatic, and its curse is more severe. The main organ involved in AE is the liver and, although multiorgan disease is relatively common (13%), extrahepatic disease is exceptional (<1%). The usual clinical picture is unspecific and may include malaise, unintentional weight loss, and abdominal pain. Hepatic syndromes like jaundice, cholangitis, portal hypertension, or Budd-Chiari syndrome may develop. The cysts usually exhibit invasive, tumor-like growth, so the lesions may resemble those of hepatocellular carcinoma or sarcoma [20].

Alveolar echinococcosis is usually diagnosed by imaging techniques in conjunction with serology. Imaging techniques usually demonstrate lesions with ill-defined limits, central necrosis, and irregular calcifications. Serologic tests have a better diagnostic performance than those available for CE.

There is no optimal evidence-based therapeutic approach for AE. The WHO has developed a PNM classification system, mimicking the TNM classification of tumors, which is useful for guiding general management [25]. The classification system stands for extension of the parasitic mass in the liver (P), involvement of neighboring organs (N), and metastases (M). Since 10-year mortality is >90% in untreated patients, the therapeutic approach requires radical surgery and very prolonged or long-life use of anthelminthics (albendazole). Liver transplantation may be considered in certain cases.

Take-Home Messages

- Invasive candidiasis is a healthcare-associated infection with life-threatening consequences. It is associated with unspecific clinical signs and its diagnosis is difficult. In the presence of risk factors, empirical antifungal treatment should be started with no delay in critical ill patients.
- Mucormycosis is a severe, devastating infection that affects diabetic, immunocompromised, and COVID-19 patients. Its diagnosis and treatment should be initiated with no delay as this infection carries high mortality rates.

- Malaria is a life-threatening mosquito-borne infectious disease caused by one or more of the species of the *Plasmodium* genus. A high degree of clinical suspicion is required, since no combination of signs or symptoms reliably distinguishes malaria from other causes of fever. The diagnosis of malaria requires the presence of fever and the identification of parasites (preferably by light microscopic examination of a blood smear). The treatment of severe malaria is a medical emergency and consists of intravenous or intramuscular artesunate for at least 24 h (3 doses of 2.4 mg/kg, given at 0, 12, and 24 h), which may be de-escalated to artemisinin-based combination therapy when parasite density is low.
- The infection caused by the larval stage of *Echinococcus granulosus* is called cystic echinococcosis or hydatidosis. Most patients exhibit liver (50–70%) or lung (20–30%) involvement and remain asymptomatic for years. Symptoms usually develop in the setting of mass effect due to the increase in the size of a cyst in a limited space. Diagnosis is based on imaging techniques in conjunction with serology. There is no optimal evidence-based therapeutic approach for cystic echinococcosis, and the management may include observation, interventional strategies, and anthelminthics (albendazole).
- The infection caused by *Echinococcus multilocularis* is called alveolar echinococcosis. The cysts usually involve the liver and exhibit invasive, tumor-like growth. Diagnosis is based on imaging techniques and serology. There is no optimal evidence-based therapeutic approach for alveolar echinococcosis but, due to its invasiveness, it usually requires radical surgery and very prolonged or long-life use of anthelminthics (albendazole).

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Severe Malaria in the ICU

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Contents

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Learning Objectives

- Recognize the main manifestations of uncomplicated and severe malaria.
- Describe the diagnosis and treatment of malaria.
- Recognize the complications of severe malaria that warrant intensive care management.

14.1 Introduction

Malaria is an endemic disease of tropical and subtropical regions, caused by any of the species of the parasite of the genus *Plasmodium* and transmitted by the bite of the female *Anopheles* mosquito. In Spain, malaria is the most important imported parasitic disease, and *Plasmodium falciparum* is the predominant species (more than 80% of the cases) [1]. There are two disease presentations of malaria: uncomplicated and severe.

Severe malaria is acute malaria with major signs of organ dysfunction and/or high level of parasitemia. Most cases of severe malaria are attributable to *P. falciparum* (90%). The risk of morbidity and mortality is variable, and depends on early diagnosis and treatment [1]. Admission to an Intensive Care Unit (ICU) may be necessary for supportive care and to manage life-threatening complications of the disease.

Case Presentation

We present the case of a 48-year-old male patient, who works as a missionary and spends long periods of time in Mozambique. His past medical history was remarkable for up to 4 previous episodes of malaria, the last one 9 months before, which was treated with atovaquone-proguanil.

He presented to the Emergency Department with a 5-day history of fever, headache, and arthralgia. His physical examination showed lymphangitis in the left leg, in relation to an insect bite. He had returned from Mozambique 4 days earlier and claimed to have received several cycles of chemoprophylaxis against malaria. He was admitted to the Internal Medicine ward for study, confirming infection by *Plasmodium falciparum*, after which treatment with atovaquone-proguanil was initiated. After 4 days of admission, acute neurological worsening occurred, with confusional symptoms and altered level of consciousness, together with tachycardia, petechiae in the lower limbs, and analytical worsening (renal, hepatic, and hematological dysfunction). The patient was transferred to the ICU due to this deterioration.

14.2 Investigations

Physical examination on admission: Glasgow Coma Scale 13, disoriented and bradypsychia. Cranial nerves without alterations. Preserved strength and sensitivity. Normal blood pressure (110/75 mmHg), sinus tachycardia 100 bpm, eupneic with $satO_2$ 95% on room air. Petechiae in the lower limbs.

Parasitological study: Day 0 (hospital admission): positive antigen and Giemsa stain for *P. falciparum*. fifth day (ICU admission): positive antigen and Giemsa stain for *P. falciparum*. Sixth day: positive antigen for *Plasmodium* but negative Giemsa stain. Seventh day: negative parasitological study.

Laboratory: Fifth day (ICU admission): leukocytes 4200/mcL (76%N), hemoglobin 12.6 g/dL, platelets 40,000/mcL, TP 91%, INR 1.06, fibrinogen 757 mg/dL, sodium 130 mmol/L, potassium 3.8 mmol/L, glucose 124 mg/dL, creatinine 1.67 mg/dL, urea 57 mg/dL, total bilirubin 5.05 mg/dL, direct bilirubin 1.89 mg/dL, GOT 84 U/L, GPT 93 U/L, LDH 601 U/L, PCR 327 mg/L, procalcitonin 18.28 ng/dL. Venous blood gas: pH 7.38, pCO_2 38 mmHg, bicarbonate 22 mmol/L, lactate 3.6 mmol/L.

Brain CT scan: Fifth day (ICU admission): without acute structural pathology.

Electroencephalogram (EEG): Fifth day (ICU admission): diffuse cortical alteration with slowing of brain bioelectric activity of moderate intensity, without interhemispheric asymmetries or paroxysmal epileptiform abnormalities.

Abdominal ultrasound: Sixth day (ICU day 1): Liver with diffusely altered echogenicity with patchy steatosis. Splenomegaly 14 cm, of homogeneous echogenicity.

Brain magnetic resonance (MR): Seventh day (ICU day 2): without structural pathology.

Microbiology: Negative blood cultures, hepatotropic viruses, HIV, and SARS CoV-2.

Funduscopic exam: Absence of malarial retinopathy signs.

14.3 Differential Diagnosis

It is important to consider malaria in all febrile patients with history of travel to malaria-endemic areas. The differential diagnosis must be made with other diseases or syndromes that are acquired in endemic areas and have fever as the main symptom: dengue fever, chikungunya, or leptospirosis. The diagnosis is established with serology.

In addition, the differential diagnosis included other infectious diseases that occur with fever, tachycardia, and headache, like meningitis, pneumonia, or sepsis due to bacteremia. The differential diagnosis requires drawing blood cultures, sputum culture, culture of cerebrospinal fluid, etc.

14.4 Treatment

Upon admission to the ICU, antiparasitic treatment with intravenous artesunate was started. When clinical improvement was achieved, it was changed to oral dihidroartemisin-piperaquine, until the course was completed.

Supportive therapies were required for the management of the associated complications, including invasive mechanical ventilation, low-dose vasoactive drugs, continuous veno-venous hemodialysis, and transfusion of blood products (platelets and red blood cells). The patient received an empirical antibiotic course with meropenem, linezolid, and fluconazole.

14.5 Evolution, Outcome, and Follow-up

The patient was admitted to the ICU after a 4-day stay on the hospital ward, due to clinical and laboratory signs of severe malaria. Intravenous antiparasitic treatment was initiated, with daily monitoring of the parasite density by the Department of Hematology. Parasitemia disappeared 48 h later, both in Giemsa stains and the antigenic tests.

During the evolution, the patient presented the following complications:

- Neurological failure, requiring invasive mechanical ventilation and sedation for 7 days. A brain CT scan, brain MR, and EEG ruled out structural pathology and epileptiform activity. Funduscopic exam ruled out malarial retinopathy. Progressive improvement of the confusional state was achieved, being the patient asymptomatic at discharge.
- Liver failure, with peak levels of bilirubin, transaminases, and LDH 48 h after ICU admission and progressive decline until resolution.
- Oliguric kidney failure, with creatinine higher than 4 md/dL, requiring continuous veno-venous hemodialysis for 48 h and subsequently controlled with diuretics.
- Hematological failure, with thrombocytopenia requiring platelet transfusion and hemolysis of mixed cause (in relation to the infection and the antiparasitic treatment), which required several transfusions of packed red blood cells, without associated serious bleedings during the process. Splenomegaly was identified on abdominal ultrasound.

After 10 days of ICU care, the patient was discharged back to the Internal Medicine ward, with no associated organ dysfunction except hemolysis and non-oliguric kidney dysfunction. These dysfunctions resolved before hospital discharge, 12 days later, with no added complications.

14.6 Discussion

Criteria for severe malaria are defined by the World Health Organization (Table 14.1). The most common manifestations of severe malaria (and the most frequent reason for needing admission to the ICU) are cerebral malaria, acute lung

Table 14.1 Definition of severe Malaria: one or more of the above criteria, occurring in the presence of malaria infection and in the absence of an identified alternative cause. Data from: World Health Organization. Guidelines for malaria. WHO: Geneva 2022

Manifestations	Definitions
Impaired consciousness	Glasgow coma score < 11 in adults or Blantyre coma score < 3 in children; inability to swallow
Prostration	Generalized weakness so that a person is unable to sit, stand, or walk without assistance
Multiple convulsions	More than two episodes within 24 h
Acidosis	A base deficit of >8 mEq/L, a plasma bicarbonate level of <15 mmol/L, or venous plasma lactate ≥5 mmol/L. Clinical indicators of acidosis include rapid, deep, labored breathing
Hypoglycemia	Blood or plasma glucose <40 mg/dL (<2.2 mmol/L) for children ≥5 years and adults; blood or plasma glucose <54 mg/dL (<3 mmol/L) for children <5 years
Severe anemia	Hemoglobin concentration ≤ 5 g/dL or hematocrit ≤15% in children <12 years of age (<7 g/dL and <20%, respectively, in adults) with parasite count >10,000 parasites/uL
Renal impairment	Plasma or serum creatinine >3 mg/dL (265 umol/L) or blood urea >20 mmol/L
Jaundice	Plasma or serum bilirubin >50 umol/L (3 mg/dL) with one of the following: *Plasmodium falciparum* parasite count >2.5% parasitemia; *Plasmodium knowlesi* parasite count >20,000 parasites/u
Pulmonary edema	Radiographically confirmed or oxygen saturation < 92% on room air with respiratory rate > 30/min, often with chest in drawing and crepitation on auscultation
Significant bleeding	Including recurrent or prolonged bleeding (from the nose, gums, or venipuncture sites), hematemesis, or melena
Shock	Compensated shock is defined as capillary refill ≥3 s or temperature gradient on leg, but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mmHg in children or < 80 mmHg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
Hyperparasitemia	*P. falciparum*: In nonimmune travelers: Parasitemia ≥5%, all patients: Parasitemia >10%

injury, which can progress to acute respiratory distress syndrome (in up to 25% of cases), acute kidney injury, typically presenting as acute tubular necrosis, and acidosis [2]. For its diagnosis, the presence of one of these manifestations is sufficient, but it is more common for them to be combined in the same patient. Renal dysfunction is an independent predictor of a poor outcome [3]. Anemia is the most common

hematologic abnormality, and it is usually mild to moderate, though severe anemia may occur in the setting of *P. falciparum* malaria. Anemia in the context of malaria may appear as a result of the following factors: hemolysis of parasitized red cells, increased splenic sequestration and clearance of erythrocytes with diminished deformability, cytokine suppression of hematopoiesis, shortened erythrocyte survival or repeated infections, and ineffective treatments. Liver dysfunction is more common among adults than among children. Other complications are splenic rupture and bacterial coinfection, for which it is recommended to obtain cultures and associate empirical antibiotic therapy.

Initial treatment of severe malaria consists of parenteral therapy. During treatment, parasite density should be monitored every 12 h during the first two to three days, in order to document declining parasite density and to confirm adequate response to therapy [4].

The risk of death due to severe malaria is greatest in the first 24 h after clinical presentation. Early diagnosis is essential. In a patient living in or coming from an endemic area with fever or other infectious symptoms, malaria should be ruled out. If severe symptoms appear, the diagnosis should be made even faster and, when in doubt, treatment should be started as soon as possible.

Take-Home Messages

- Intensive care physicians should consider malaria in all febrile patients with a history of travel to malaria-endemic areas.
- The most common manifestations of severe malaria are cerebral malaria, acute lung injury, acute kidney injury, and acidosis.
- Treatment of severe malaria should be early and intravenous.

Summary

Severe malaria is acute malaria with major signs of organ dysfunction and/or high level of parasitemia, which sometimes requires admission to an Intensive Care Unit (ICU).

We present the case of a young patient who had returned from Mozambique 4 days before. He reported a 5-day history of fever, headache, and arthralgia. Parasitological study confirmed infection by *P. falciparum* and treatment with atovaquone-proguanil was initiated.

After 4 days of admission, acute neurological worsening together with renal, hepatic, and hematological dysfunction occurred, requiring transfer to the ICU. Intravenous antiparasitic treatment was started, with daily monitoring of the parasite density until its disappearance 48 h later. In ICU complications included neurological failure (requiring invasive mechanical ventilation), liver failure, renal failure (requiring continuous veno-venous hemodialysis), and hematological failure. After 10 days of ICU care and a 12-day stay in the Internal Medicine ward, he was discharged without organic dysfunctions.

Criteria for severe malaria are defined by the World Health Organization. The most common manifestations are cerebral malaria, acute lung injury, acute kidney injury, and acidosis. In a patient living or coming from an endemic area with fever or other infectious symptoms, malaria should be ruled out as soon as possible. The risk of death due to severe malaria is greatest in the first 24 h after clinical presentation, so early diagnosis and treatment are essential.

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Parasitic Infections. Dyspnea, Edema, and Abdominal Distention

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Contents

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Learning Objectives

- Clinical and diagnostic approach to hydatid disease.
- Differential diagnosis of hepatic cysts.
- Treatment of echinococcosis.

15.1 Introduction

Human hydatid disease or cystic echinococcosis is a life-threatening zoonotic disease that exists worldwide. It is caused by a parasite genus *Echinococcus*. Humans and cattle are intermediate hosts that acquire the disease by ingesting the eggs. Those eggs reach the liver nesting and forming cysts which are the adult form of the parasite. Four *Echinococcus* species are capable of infecting humans. *E. granulosus* and *E. multilocularis* are the most common, causing cystic echinococcosis (CE) and alveolar echinococcosis (AE) [1].

The clinical presentation of *E. granulosus* infection depends upon the locations of the cysts and their size. Symptoms are related to mass effect within organs, obstruction of blood or lymphatic flow, or complications such as rupture in the pleural or peritoneal cavity, which may lead to anaphylactic shock.

Echinococcosis treatment involves an antiparasitic drug combined with either surgical resection of the cyst or percutaneous aspiration. The outcome depends on the stages of the disease (see Table 15.1) [1].

Table 15.1 World Health Organization (WHO) diagnostic classification

WHO stage	Description	Stage	Size	Preferred treatment	Alternate treatment
CE1	Unilocular unechoic cystic lesion with double line sign	Active	<5 cm	Albendazole alone	PAIR
			>5 cm	Albendazole + PAIR	PAIR
CE2	Multiseptated, "rosette-like" "honeycomb cyst"	Active	Any	Albendazole + surgery	Modified catheterization
CE3a	Cyst with detached membranes	Transitional	<5 cm	Albendazole alone	PAIR
			>5 cm	Albendazole + PAIR	PAIR
CE3b	Cyst with daughter cysts in solid matrix	Transitional	Any	Albendazole + surgery	Modified catheterization
CE4	Cyst with heterogeneus contents	Inactive	Any	Observation	–
CE5	Solid plus calcified wall	Inactive	Any	Observation	–

Case Presentation

A 65-year-old female, without relevant medical or surgical history and no chronic medications. She denies contact with animals.

The patient came to the emergency room with a 15-day history of progressive dyspnea until becoming at rest, lower extremity oedema and abdominal distention. Initial examination revealed right pulmonary hypoventilation, ascites and oedema with fovea on the legs.

Chest X-ray exhibited a complete whitening of the right hemithorax. Therefore, a chest CT scan was performed, showing a giant solid-cystic mass in the right hepatic lobe with pleural involvement, compatible with a hydatid cyst ruptured into the pleural cavity (see ▶ Sect. 15.2).

The patient was examined by the surgery team rejecting an initial surgical approach. A thoracentesis was performed and a right chest tube was placed, with an outflow of 3 L of purulent appearance, similar to grape's skin. Pleural fluid samples were sent to microbiology. A paracentesis was also performed and ascites samples were sent for analysis. The patient suffered respiratory worsening in the Emergency Room, with requirement of no-invasive ventilation (NIV) support, and she was admitted to the ICU.

15.2 Investigations

15.2.1 Complementary Images

- **First chest X-Ray**: A massive pleural effusion is observed in the right lung (see ◘ Fig. 15.1).
- **First CT**: A large solid-cystic mass is observed, which caused right lung collapse. This mass shows a homogeneous and hypodense density, two important characteristics of hydatid cyst (see ◘ Fig. 15.2).
- **Control CT (days 13th and 27th)**: A poor evolution of respiratory distress and the hepatic hydatic cyst with right pleural fistulation is observed in these slices (see ◘ Fig. 15.3).

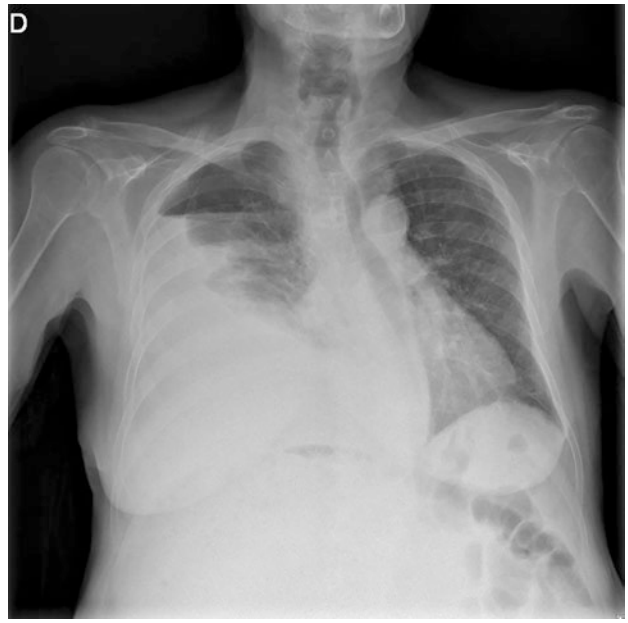

Fig. 15.1 First X-ray in emergency room

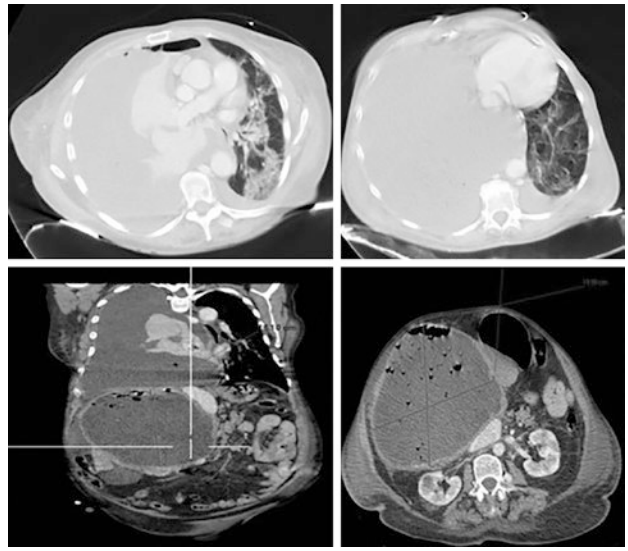

Fig. 15.2 First CT in emergency room

15.2.2 Blood Tests

- Blood tests were taken daily. Liver enzymes, white blood cell count, and acute phase reactants were elevated.

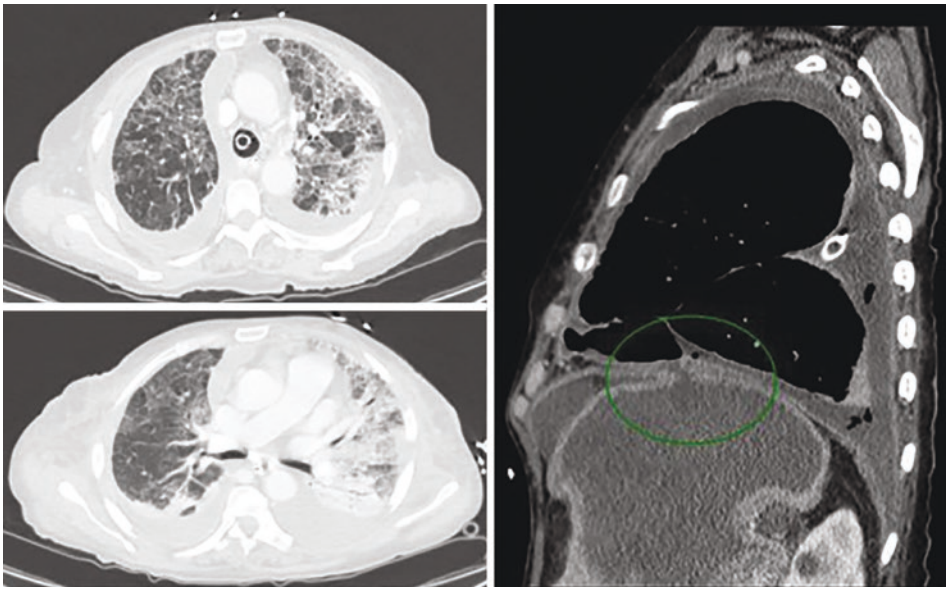

Fig. 15.3 Control CT (days 13th and 27th)

Fig. 15.4 Macroscopical and microscopical *E. granulosus* in pleural fluid

15.2.3 Microbiological Tests

- Pleural fluid: *E. granulosus* isolated (see Fig. 15.4).
- Bronchial aspirate: *S. maltophila* isolated.

15.3 Differential Diagnosis

For patients without risk factors for a malignant hepatic lesion, the initial diagnostic evaluation is primarily based on the imaging appearance of the incidental lesion. Some liver lesions can be diagnosed based on noncontrast ultrasound, while other lesions require further diagnostic evaluation based on lesion characteristics. Some examples of solid liver lesions are described below:

- **Simple benign cyst:** It appears as an anechoic unilocular fluid-filled space with smooth margins and posterior acoustic enhancement
- **Hepatic hemangioma**: It is diagnosis may be suspected in a patient without cirrhosis who is found to have a solid liver lesion on imaging. It is seen in the ultrasonography with a homogeneous, hyperechoic, and well-delineated margin.
- **Hepatocellular carcinoma**: It is an insidious disease, whose diagnosis is based on clinical history and imaging. It typically demonstrates a non-rim arterial phase hyperenhancement relative to the liver parenchyma in contrast CT.
- **Polycystic liver disease**: It is a rare genetic disorder diagnosed by family history, molecular test, and ultrasound.
- **Hepatic abscess**: It may resemble an *Echinococcus* cyst clinically and radiographically. Liver abscess is examined by aspiration. If echinococcosis is suspected, percutaneous aspiration or biopsy should be performed only when other diagnostic methods come inconclusive, due to a potential risk for anaphylaxis and secondary dissemination.

Our main clinical suspicion was echinococcosis due to the findings of a large intrahepatic anechoic cyst occupying the entire right hepatic lobe associated with pleural effusion along with cysts and detritus, possibly by fistulation and spread of the hepatic cyst content into the pleural cavity.

However, until microbiological confirmation of *E. granulosus* in pleural fluid, we treated the patient with both albendazole and amoxicillin/clavulanic acid to cover a bacterial hepatic abscess, as a second diagnostic option.

15.4 Treatment

The clinical approach depends on the World Health Organization (WHO) diagnostic classification (see Table 15.1). The standard of treatment for echinococcosis is antiparasitics combined with surgical resection of the cyst or percutaneous aspiration.

- **Antiparasitic treatment**: Albendazole is the primary antiparasitic agent for treatment of *E. granulosus*, at a dose of 15 mg/kg/day divided into two doses. The optimal duration is uncertain; one to 3 months may be appropriate.
- **Surgery**: Is the treatment of choice for the management of complicated cysts. Antiparasitic therapy is mandatory for at least one-week prior surgery to minimise the risk of secondary echinococcosis in case of cyst rupture or leak.

- **Percutaneous management**: Puncture, aspiration, injection, and respiration (PAIR), which is usually effective for single cyst rather than multiple cysts. Percutaneous treatment is associated with risk for anaphylaxis from 0.3 to 1.6%. As in surgery, antiparasitics should be administered at least 4 days before PAIR and continued for 3 months after the procedure.

In our case, we started empirical treatment with albendazole and amoxicillin/clavulanic acid to cover the other possible diagnosis of bacterial abscess. Once the etiology was confirmed, we discontinued the antimicrobial and maintained albendazole (15 mg/kg/day, divided into two doses).

From the surgical point of view, the possibility of surgical intervention was considered 1 week after albendazole treatment, which is required to prevent disease dissemination. But, when the time came, the surgery team rejected the surgical approach due to the extent of the disease and the clinical situation of the patient, who had severe pulmonary involvement evolving to acute respiratory distress syndrome (ARDS). PAIR was also proposed, but was not possible due to the presence of several cysts associated with the main giant cyst.

15.5 Evolution, Outcome, and Follow-up

During ICU stay, our patient suffered a progressive hypercapnic respiratory failure even under noninvasive ventilatory support, requiring orotracheal intubation and invasive mechanical ventilation on the second week of admission.

Pulmonary damage continued worsening, and the patient developed ventilator-associated pneumonia due to *Stenotrophomona maltophila*. Percutaneous tracheostomy was performed after the ninth day of intubation.

She was hemodynamically unstable in the first days. Invasive hemodynamic monitoring parameters were compatible with septic shock, requiring high doses of noradrenaline and resuscitation with crystalloids, improving during her stay and allowing vasopressor withdrawal.

She alternated sinus rhythm with two episodes of atrial fibrillation with a ventricular rate of 150 beats per minute, treated with amiodarone and electrical cardioversion on one of the episodes due to hemodynamic instability.

The patient developed severe bilateral pulmonary fibrosis, with refractory respiratory acidosis despite protective mechanical ventilation parameters.

Because of the ominous progression of respiratory failure, the medical team decided to withdraw care due to futility and the patient died on her fourth week of admission.

15.6 Discussion

As observed in this case, hepatic hydatid disease may involve the diaphragm and spread into the thoracic cavity. The lack of a peritoneal covering over the bare area of the liver makes it less resistant to cyst growth and more vulnerable to a trans-

diaphragmatic extension of hepatic hydatid cysts. The air within hepatic or diaphragmatic hydatid cysts should raise the possibility of bronchial communication, especially if associated with parenchymal involvement of the adjacent lung. The association of pleural effusions, atelectasis, or pulmonary consolidation is suggestive findings of thoracic involvement [2].

As demonstrated in our clinical case, a CT scan is valuable for the detection and assessment of trans-diaphragmatic extension and extension of hepatic hydatid cysts into the thoracic cavity. There is a proposed surgical grading of diaphragmatic or trans-diaphragmatic thoracic involvement in hepatic hydatid disease based on the degree of cyst evolution and involvement [3]:

- Grade 1: Firm adherence between the diaphragm and the cyst surface without diaphragmatic perforation.
- Grade 2: Diaphragmatic perforation with minimal invasion of the thoracic cavity.
- Grade 3: Diaphragmatic perforation associated with either cyst growth inside the thoracic cavity or daughter cysts seeding.
- Grade 4: Involvement of the lung parenchyma by communication between the cyst and the bronchial tree or compression of the lung parenchyma.
- Grade 5: Broncho-biliary fistula formation.

In our case the patient complies with a grade 4.

The surgical approach of trans-thoracic extension with diaphragmatic perforation is complex and may include bronchial fistula ligation if it appears, lung segmentectomy or lobectomy, decortication, and diaphragmatic repair, as well as treatment of the underlying hepatic hydatid cysts. Placement of abdominal and thoracic drainage tubes may be necessary, like in our case [4].

Despite the outcome of this clinical case and the rejection by the surgical team due to the patient's morbidity and mortality risks, we consider that it is interesting because there are a few clinical cases reported in the literature of hepatic hydatid cyst complicated by trans-diaphragmatic rupture, and none of them was associated with severe respiratory distress that would hamper the therapeutic approach.

Take-Home Messages

- Hydatid cyst is a multifaceted disease that can be lethal if it is not diagnosed and treated early.
- Medical treatment with albendazole is followed by interventional treatment, either surgically or PAIR.
- It is important to make a differential diagnosis with any other cause of liver space-occupying lesion, mainly bacterial abscess.

Summary

The hydatid disease is a zoonosis caused by the larvae of *Echinococcus granulosus*, which remains a health problem worldwide. Treatment of echinococcosis requires antiparasitics and surgical resection of the cyst or percutaneous aspiration. Complications occur mainly from compression of structures, anaphylaxis due to cyst rupture, obstruction of lymphatic and blood flow.

We report a case of a 65-year-old female who consulted the Emergency Room for dyspnea at rest and abdominal distension of 15 days of duration. Radiological findings on chest X-ray and CT were compatible with a hydatid cyst in the right hepatic lobe with possible fistulation to the right pleura. The microbiological diagnosis was confirmed when *E. granulosus* was isolated in pleural fluid.

In this case, the giant liver cyst that grew insidiously manifested by compromising ventilation due to spread to thoracic cavity and lung involvement.

The patient was admitted to the ICU due to respiratory failure requiring NIV support. Medical treatment was started with albendazole and the case was discussed with the surgery team, who rejected a surgical approach given the extent of the disease and the patient's pulmonary involvement. PAIR was also planned, but was not possible due to the presence of several lesions associated with the main cyst. She suffered progressive respiratory deterioration with hypercapnia requiring orotracheal intubation in the second week of admission. A new chest CT scan showed advanced pulmonary fibrosis and signs of VAP. Finally, after 1 month of ICU stay, the patient died after withdrawal of care due to refractory respiratory failure.

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An Unusual Cause of Intracranial Hemorrhage: Cerebral Mucormycosis

Yelco Chicote Carasa and Laura López García

Contents

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Learning Objectives

- To consider diabetes mellitus as a cause of immunosuppression, especially in patients with poor glycemic control.
- To always look for the etiology of intracranial bleeding and not to be carried away by appearances.
- To suspect fungal infection as a cause of neuroinfection in the immunocompromised patient.
- To illustrate a case of apparent hemorrhagic stroke, in which the correct diagnosis arises from brain histopathology.
- To highlight the management of refractory intracranial hypertension, including to decompressive craniectomy and barbiturate coma.

16.1 Introduction

Mucormycosis is a fungal infection caused by filamentous fungi belonging to the order Mucorales. These are ubiquitous fungi that mainly affect severely immunocompromised hosts. The location of the disease varies according to the type of immunosuppression. Onco-hematological malignancies are the main risk factors in developed countries, while diabetes mellitus accounts for the majority of cases in developing areas [1].

Invasive mucormycosis includes different clinical entities, depending on the affected organs: gastrointestinal, cutaneous, renal, pulmonary, and rhino-orbito-cerebral mucormycosis. It is a relatively rare pathology, with variable incidences among different countries and populations [2].

The diagnosis of mucormycosis still relies on microbiological analyses of tissues obtained by surgical debridement or biopsy. Visualization of nonseptate broad hyphae with branching at right angles on direct microscopy strongly suggests infection with Mucorales [3]. Serum fungal biomarkers such as β-D-glucan and galactomannan are not relevant to the diagnosis. In recent years, new diagnostic tools have emerged, such as polymerase chain reaction (PCR) or mass spectrometry-based techniques, although their performance is still inferior to that of classical histopathological and microbiological tests [1].

As for treatment, it is based on two essential pillars: surgical debridement, which should be aggressive if possible; and systemic antifungal therapy, usually with a combination of liposomal amphotericin B and an azole with activity against Mucorales (isavuconazole or posaconazole) [4].

Mortality varies significantly depending on the location of the lesions. For example, according to the literature, mortality of rhino-orbito-cerebral mucormycosis varies between 25 and 60%, with better outcomes when limited to the paranasal sinuses, and higher mortality in case of angioinvasion and infiltration of central nervous system [2].

Case Presentation

A 44-year-old man, from Honduras, with a personal history of poorly controlled diabetes mellitus (DM), presented to the emergency department with deteriorating level of consciousness. He had consulted at another hospital for somnolence and was diagnosed with diabetic ketoacidosis three days before. He was discharged after 24 h, once the acidosis was resolved and the insulin treatment was optimized.

Upon arrival to our hospital, he was tachycardic, tachypneic, and febrile, with normal arterial blood pressure. He was comatose (Glasgow coma scale (GCS) of 7 points) with risk of bronchial aspiration. A venous gas blood analysis was performed, demonstrating metabolic acidosis with a pH of 7.26 and a bicarbonate of 11 mmol/L.

Given the situation, the patient was intubated for mechanical ventilation and was admitted to the intensive care unit (ICU).

16.2 Investigations

After initial stabilization, a computed tomography (CT) was performed, which revealed a large bilateral cerebral hemorrhage in the basal ganglia open to the ventricular system. It was associated with perilesional edema and an 8-mm midline shift. CT angiography was also obtained, which ruled out large vessel occlusion or vascular malformation (Fig. 16.1).

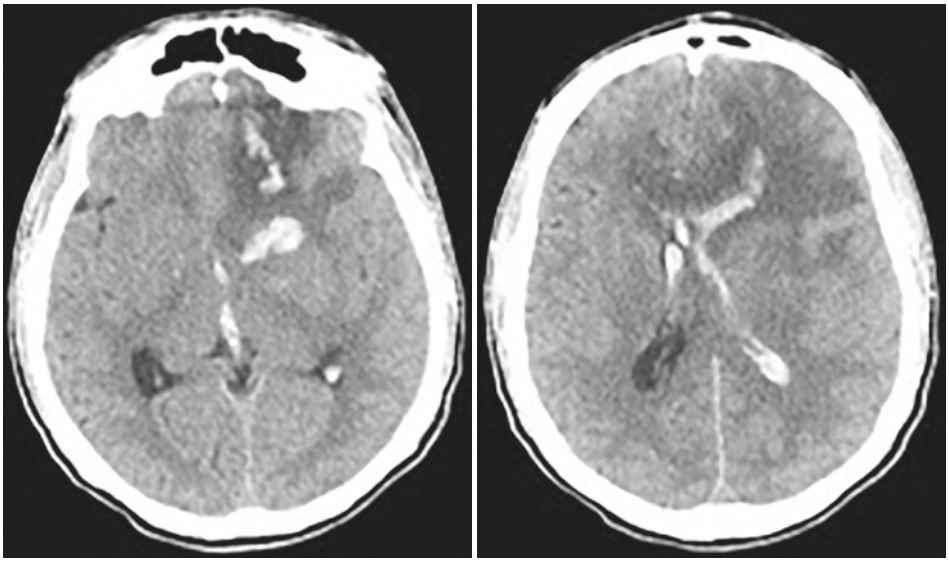

Fig. 16.1 CT scan showing intraparenchymal hemorrhage in the basal ganglia and left frontal lobe open to the ventricular system, with mass effect and midline shift

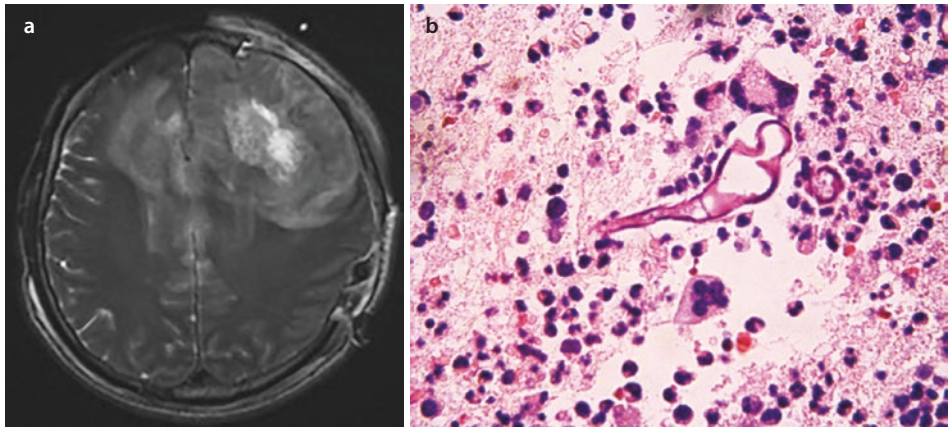

Fig. 16.2 **a** MR sequence T2 flair in axial cut showing bihemispheric involvement. **b** Mucor hyphae invading the cerebral parenchyma

Standard diagnostic tests (electrocardiogram, chest radiograph, and basic laboratory panel) revealed no abnormalities.

Neurosurgery was consulted, and the patient underwent urgent surgery to evacuate the hematoma; because of signs of herniation, the cranial vault bone was not replaced. Cerebral parenchyma samples were collected and sent to the laboratory for histopathological and microbiological analysis. During the procedure, indirect signs of venous sinus thrombosis were observed. A venous phase contrast-enhanced CT was performed after the intervention, which ruled out thrombosis of the venous system. Due to the persistence of radiological signs of intracranial hypertension, a parenchymal fiberoptic bolt was placed to invasively monitor his intracranial pressure (ICP).

Given that the etiology of the bleeding was not clarified, a cerebral magnetic resonance imaging (MRI) was ordered in the following days. It demonstrated extensive frontal cerebral parenchymal involvement, associated with cortical and subarachnoid hemorrhages, as well as images suggesting thrombosis of the venous sinus and cortical veins (Fig. 16.2A).

16.3 Differential Diagnosis

The differential diagnosis in this case includes the following:

- Vascular causes. This patient suffered from altered consciousness and a hemorrhagic stroke on imaging tests. The first clinical suspicion was an undiagnosed arterial hypertension. Likewise, in the MRI, there were signs of unnoticed venous thrombosis in venous phase CT, but they were incomplete thrombosis and, due to their topographic locations, they did not fully justify the involvement of all the damaged brain territories. The initial syndromic diagnosis was malignant cerebral infarction, with the suspicion that diabetic ketoacidosis was a secondary event.

- Infectious causes. Our patient was an immunocompromised individual because of his DM. The various etiologies of central nervous system (CNS) infection can begin with a nonspecific neurologic deterioration and, although rarely, can cause different types of intracranial bleeding, especially the fungal causes due to their tendency to angioinvasion, generating thromboses and hemorrhages along their progression.
- Immune mediated diseases. Within this group, we include immune mediated aseptic encephalitis, like anti-NMDA receptor encephalitis. These are rare etiologies, usually difficult to diagnose and with significant morbidity and mortality.

16.4 Treatment

The patient was admitted to the ICU, where neurocritical care was initiated, including sedation, analgesia, temperature control, and escalation to the barbiturate coma for optimization of cerebral perfusion pressure.

In addition, given the diabetic ketoacidosis that was observed upon admission, treatment of the latter was initiated with fluid and electrolyte administration, intravenous insulin, glycemic control, and ketonemia monitoring.

The surgeons evacuated the hematoma without bone replacement, leaving a large decompressive craniectomy. Following the CT scan performed 24 h after the surgery, which showed persistent signs of intracranial hypertension, a second neurointervention was performed during which biopsies were taken and a parenchymal fiberoptic bolt was placed.

Besides, given the suspicion of neuroinfection as one of the etiologies (lesion distribution on CT, not corresponding to vascular territories, and its infiltrative nature) empirical antimicrobial therapy was initiated. Antimicrobial therapy included meropenem 2 g every 8 h (the patient was immunocompromised and at risk of *Nocardia* infection among the possible etiologies) and linezolid 600 mg every 12 h, as well as corticosteroid therapy with dexamethasone 4 g every 6 h, taking into account the possibility of an immune-mediated encephalitis.

The patient's relatives denied recent traveling or risky behavior either nutritionally or sexually, but reported that the patient had a weeks-long history of dental and ear pain for which he did not consult. He was examined by maxillofacial surgery, and no lesions were found in the examined territory. At that point, Anatomical Pathology reported the discovery of hyphae compatible with *Mucor* in the brain biopsy (◘ Fig. 16.2B), so antibiotic therapy and corticosteroids were stopped. Dual antifungal therapy with liposomal amphotericin B and isavuconazole were started (amphotericin B at doses of 10 mg/Kg every 24 h and isavuconazole with loading dose of 200 mg every 8 h for 6 doses and, then, 200 mg daily).

16.5 Evolution, Outcome, and Follow-up

The patient was admitted to the ICU with the diagnosis of extensive intraparenchymal hemorrhage associated with a significant mass effect, so he underwent urgent surgical intervention for its evacuation, and primary decompressive craniectomy was performed. Given the severity of the lesions, invasive monitoring of intracranial pressure was decided upon. Despite progressive escalation of treatment to third-level measures (including barbiturate coma) and targeted antifungal treatment, the patient developed refractory intracranial hypertension.

In this situation, with no other available therapeutic options available, and given the unfavorable prognosis of the established lesions, probably leading to severe neurological sequelae and death, the case was reassessed in a multidisciplinary meeting and, in accordance with the relatives, the team decided to withdraw life-sustaining treatment. The patient died after 7 days in the ICU.

16.6 Discussion

Invasive mucormycosis is a potentially fatal fungal infection that predominantly affects individuals with any degree of immunosuppression. Its rhino-orbito-cerebral variation is typical of patients with poorly controlled diabetes mellitus, especially those with episodes of ketoacidosis. Involvement of paranasal sinuses is the most frequent feature, although spread to the cerebral parenchyma is not unusual. Invasive mucormycosis is an uncommon entity, but it entails high rates of mortality and disability, thus the importance of a high level of suspicion that allows early initiation of antifungal therapy is clearly related to a better prognosis [1]. In the case of our patient, his DM treatment was suboptimal, and he had suffered from several episodes of ketoacidosis.

Clinical manifestations at the beginning of the clinical course can be indistinguishable from common sinusitis. At this stage, the presence of necrotic sloughs in oral or nasal mucosa is considered a sentinel sign that should alert to the possibility of a *Mucor* infection, although it is absent in almost half of cases. Less than 50% of the patients present with fever [3]. The development of neurological symptoms (*i.e.* deterioration in the level of consciousness, focal deficits, seizures, etc.) is indicative of fungal invasion of cerebral tissue. Although the temporal evolution is variable, progression to more advanced stages can occur rapidly, even within days [1].

Regarding the radiological tests, both CT and MRI can show unspecific thickening of sinus mucosa, as well as bone destruction and orbital involvement in more advanced cases. Two unique findings occur with intracranial involvement: cavernous sinus thrombosis and internal carotid occlusion. It is also possible to observe primary involvement of cerebral tissue, frequently associating bleeding/infarction areas [2].

The symptoms of our patient were exclusively neurological; nevertheless, his relatives reported that he had suffered from odontalgia and otalgia weeks prior to the admission. Initially, the CT and MRI did not report the possibility of fungal infection (probably because the initial suspicion level was low). Bilateral parenchymal involvement and the development of venous thrombosis and hemorrhages are described in the literature.

Treatment lies in the early administration of antifungal agents, surgical debridement, and correction of the underlying metabolic or immune dysfunction. The most commonly used drugs (although not supported by randomized controlled trials) are liposomal amphotericin B and azoles with activity against Mucorales (isavuconazole and posaconazole) [4]. Aggressive surgical debridement is not recommended in cases of cerebral involvement, given the limited benefit and the high risk of sequelae. Neurosurgical intervention is indicated in cases of intracranial hypertension, obstructive hydrocephalus, and spinal cord compression [2]. As for our patient, ketoacidosis and hyperglycemia were resolved within the first few hours after receiving fluid therapy and intravenous insulin. He underwent a surgical procedure to evacuate the hematoma, and a primary decompressive craniectomy was performed, and yet he developed refractory intracranial hypertension. Antifungal agents were initiated after the finding of hyphae in the biopsy samples sent from the operating room.

Take-Home Messages

- Diabetes is a serious cause of immunosuppression.
- Once established, fungal invasion is a devastating disease with significant morbidity and mortality.
- MRI is a potentially helpful tool also in intensive care settings.
- Cerebral biopsy may be a potential diagnostic test if necessary.

Summary

Mucormycosis is a fungal infection caused by fungi belonging to the order Mucorales. It is a disease of immunocompromised patients. It presents with different clinical pictures according to the affected organ. Most cases entail high morbidity and mortality, even if optimal treatment (combining debridement surgery and antifungal) is accomplished.

We presented the case of a young patient with a history of poorly controlled diabetes mellitus who was admitted to our center with neurological symptoms and diabetic ketoacidosis, with initial diagnosis of hemorrhagic stroke.

The patient developed intracranial hypertension refractory to the escalation of measures to the third tier. During etiological search of the cause of bleeding and in the series of imaging tests, the existence of an underlying lesion not congruent with vascular affectations was revealed.

Brain biopsy was performed, and it was this test that gave the diagnostic key by showing a brain tissue completely invaded by *Mucor* hyphae. Despite the diagnosis and adjusted antifungal treatment, surgical debridement was not an option, given the extensive brain involvement and the likely significant secondary brain damage due to refractory intracranial hypertension. Therefore, the withdrawal of measures was finally agreed, and the patient died 7 days after admission to the Intensive Care Unit.

Regarding this case, it is important to highlight diabetes as a cause of immunosuppression, as well as ketoacidosis as a predisposing factor to *Mucor* infection. On the other hand, the clinical picture of invasive mucormycosis can be highly unspecific, sometimes requiring many different evaluation tools, including invasive tests, such as biopsy, in almost all of the cases.

Acknowledgements We want to thank the entire team of the ICU of our hospital and especially the Polyvalent Unit where this patient was admitted.

We would also like to thank the Department of Anatomical Pathology for courteously providing us with the histopathological images provided in the case.

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A Case of Gastroparesis and Candidemia Secondary to Gastric Ischemia

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Contents

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Learning Objectives

- To identify the risk factors for gastric ischemia.
- To make a differential diagnosis for gastric ischemia.
- To know the available treatments for gastric ischemia.
- To identify the risk factors for candidemia.
- To know the therapeutic alternatives for candidemia.

17.1 Introduction

Ischemic gastropathy is highly infrequent in daily medical practice [1]. Despite the fact that there are many patients with predisposing factors, to the best of our knowledge, very few cases have been reported in the literature. The stomach is one of the most vascularized abdominal viscera in the organism [2]. Thus, gastric ischemia is considered a rare condition. There are known causes of gastric ischemia related to toxics, mechanical factors, vascular damage, or infections [1]. However, sometimes there is no clear trigger.

Case Presentation

A 52-year-old woman presented to the Emergency Department with low level of consciousness. She had a history of advanced type 1 diabetes mellitus, complicated with chronic kidney disease, diabetic retinopathy A, and diabetic foot. After performing a brain CT-scan, she was diagnosed with hemorrhage of the right basal ganglia with tetraventricular invasion.

On the fourth day of admission to the ICU, she presented with abdominal distention, intolerance to enteral nutrition, and bloody aspirate from the nasogastric tube. An abdominal CT scan was performed, with evidence of gastric pneumatosis of ischemic origin and no vascular filling defects. Given the clinical stability, a conservative surgical approach was decided, and gastric rest with parenteral nutrition was maintained. Upper gastrointestinal endoscopy was performed, with data of ischemia at the level of the greater curvature and posterior wall of gastric body. At the same time, a nasojejunal tube was placed under endoscopic guidance. Biopsy samples were taken, being negative for malignancy. Subsequently, postpyloric percutaneous endoscopic gastrostomy (PEG) was placed to continue with enteral nutrition.

Despite initial measures, the patient continued to have digestive intolerance secondary to gastroparesis requiring parenteral nutrition for more than 30 days. Upper gastrointestinal endoscopy and abdominal CT scan were subsequently performed, ruling out new data on abdominal complications.

17.2 Investigations

The complementary diagnostic tests necessary for an early diagnosis are explained below:

- Abdominal pelvic CT scan with contrast (Fig. 17.1): Gastric chamber with linear images of air density in its interior suggestive of gastric pneumatosis. Absence of enhancement is observed in the greater gastric curvature, predominantly posterior, where it presents transmural involvement. The antro-pyloric region / first duodenal portion was slightly thickened. The presence of gas in gastroepiploic veins as well as portal gas is identified. These findings are suggestive of gastric pneumatosis, possibly of ischemic origin.
- Upper gastrointestinal endoscopy (Fig. 17.2): Mucosa of the greater curvature and posterior face of, practically, the entire gastric body with edema, erythema, and congestion, friability, and violaceous nodules. The findings were compatible with ischemic etiology as the first possibility (biopsies were taken). These findings extended distally through the antrum affecting the pylorus. Rest of the gastric mucosa had normal appearance.
- Pathological anatomy: There were several fragments of gastric mucosa that showed large areas of ischemic-type necrosis, with the presence of polymorphonuclear neutrophils, signs of edema, and hemorrhage.

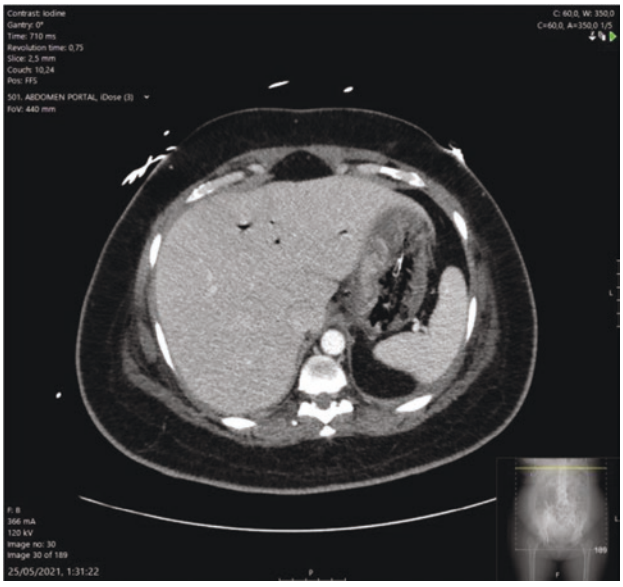

Fig. 17.1 Abdominal pelvic CT scan with contrast. The presence of gas in gastroepiploic veins as well as portal gas is identified. These findings are suggestive of gastric pneumatosis, possibly of ischemic origin

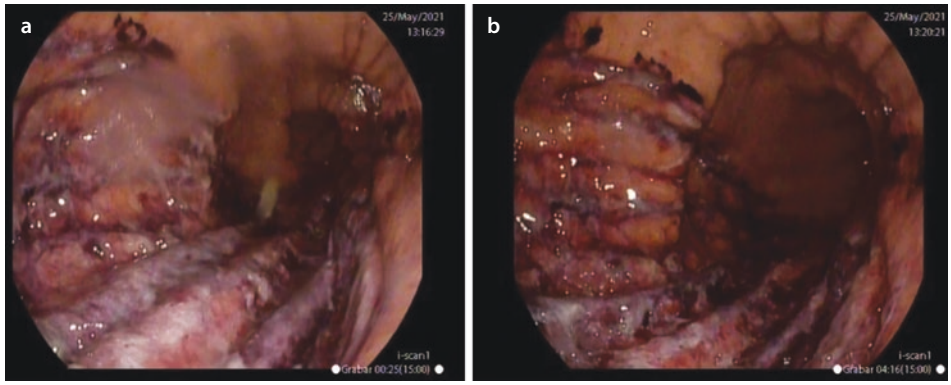

Fig. 17.2 Upper gastrointestinal endoscopy. Mucosa of the greater curvature and posterior face of, practically, the entire gastric body with edema, erythema and congestion, friability, and violaceous nodules. The findings were compatible with ischemic etiology as the first possibility

17.3 Differential Diagnosis

Etiopathogenesis, clinical features, endoscopic and radiologic findings, and patient outcomes are not well known due to the rarity of this condition [3].

The intake of toxins, medication, autoimmune diseases, or postoperative complications were discarded as a possible etiopathogenesis through a meticulous anamnesis. Bacterial growth, as the cause of the disease, was not evident in the analysis of the biopsy samples. For the reasons mentioned above, it was established that the most likely causes of the massive gastric ischemia were the patient's previous conditions of diabetes mellitus and vasculopathy.

Typically, the most common clinical manifestations of gastric ischemia are abdominal pain, emesis, enteral nutrition intolerance, or those derived from a complication, such as intestinal obstruction or perforation. Physical findings can be abdominal distension, tympanism, and tenderness [4].

In our case, the symptoms that led us to suspect gastric ischemia were abdominal distension and intolerance to enteral nutrition. There are many possible causes of such nonspecific symptom as abdominal distension: intestinal obstruction adhesions, malignancy motility disorder, diabetes mellitus, scleroderma, intestinal pseudo-obstruction, medications, irritable bowel syndrome, malabsorption, lactose intolerance, fructose intolerance, celiac disease, pancreatic insufficiency, infectious disease, small intestinal bacterial overgrowth, giardiasis, psychological, and anxiety (aerophagia). Therefore, it is important to have a high clinical suspicion and rely on diagnostic tests. On the other hand, possible causes of intolerance to enteral nutrition include bowel obstruction, severe and protracted ileus, major upper gastrointestinal bleeding, intractable vomiting or diarrhea, severe hemodynamic instability, gastrointestinal ischemia, and a high output fistula.

17.4 Treatment

There is no clearly defined treatment modality. Patients are usually treated conservatively unless signs of perforation, sepsis, or persistent bleeding (despite endoscopic intervention) are developed, in such case gastrectomy is warranted [4].

When gastric ischemia is suspected, surgical therapy must be emergent and aggressive because mortality is high for delayed diagnosis. Gastric resection with gastrojejunal or esophagojejunal anastomosis is the procedure of choice if the patient's hemodynamic condition allows it. Our patient was hemodynamically unstable due to septic shock related to catheter-related candidemia. For this reason, anastomosis was rejected in the first time. In any case, despite early surgery, the mortality estimated in a patient with massive acute gastric ischemia is greater than 50%–60%.

17.5 Evolution, Outcome, and Follow-up

After more than 3 months of admission, with multiple risk factors such as central venous catheter, acute kidney injury, parenteral nutrition, use of broad-spectrum antibiotics, and invasive devices, the patient presented with septic shock. *Candida albicans* was isolated in blood cultures and at the tip of the central venous catheter. It was decided to combine anidulafungin and liposomal amphotericin B to treat the candidemia. For treating candidemia in critically ill patients, combinations with liposomal amphotericin, voriconazole, or caspofungin are currently indicated [5, 6]. It is important to note that in severely ill patients with different organ dysfunctions, the different combinations antifungal drugs do not present a greater risk of side effects than monotherapy regimens [5, 6]. Finally, despite all the treatments and support measures, the patient developed multiple organ failure that led her to death on the 34th day of admission to unit.

17.6 Discussion

Very few cases of gastric ischemia have been described in the literature to date. There are many causes that can trigger this condition such as diabetes mellitus, viral infections, medications, postoperative complications, neurologic diseases, autoimmune diseases, or idiopathic. Thus, it is essential to elaborate a meticulous anamnesis due to the nonspecific symptoms with which this disease can be manifest.

Relying on diagnostic tests is important to identify the gastric ischemia as soon as possible. Endoscopy and CT-scan imaging play an important role in its diagnosis. Our patient developed abdominal distension and intolerance to enteral nutrition, this led us to suspect gastric ischemia. So, both upper gastrointestinal endoscopy and an abdominal CT scan were performed and confirmed the diagnosis of gastric ischemia.

The patient's clinical situation and the occurrence of possible complications will define treatment; thus, it will influence patient's prognosis. Our patient was hemodynamically unstable due septic shock, for this reason anastomosis was rejected in the first time. However, despite early surgery, the estimated mortality in a patient with massive acute gastric ischemia is greater than 50–60%.

Despite gastric ischemia is uncommon and likely underrecognized, it has a high mortality rate. For this reason, risk factors, possible causes, and the different therapeutic options available for gastric ischemia must be thoroughly evaluated in order to reach a timely and accurate diagnosis to provide patients with an appropriate treatment [3].

We must not forget that the rate of invasive candidemia and subsequent septic shock is an entity with a significant number of cases in ICU.

The highest risk factors identified for the development of Candidemia in non-neutropenic patients were intravenous catheters, complicated major abdominal surgery, parenteral hyperalimentation, antibiotic treatment for more than 14 days, body burns >50%, *Candida* isolation in more than two sites, and more than 4 days of admission.

Take-Home Messages

- It is important to consider all the possible causes of gastroparesis. Diabetes mellitus, viral infections, medications, postoperative complications, neurologic diseases, autoimmune diseases, or idiopathic should be included in the in the differential diagnosis.
- For patients with a history of starvation and/or wasting who have contraindications to enteral nutrition that are expected to persist for a week or more, we will at times initiate parenteral nutrition before 1–2 weeks have elapsed. Effects of parenteral nutrition in such patients are unknown; however, our rationale is that failure to treat the starvation in patients with little reserve will result in a worsening of their state of malnutrition, which is associated with increased morbidity.
- The treatment for gastric ischemia can be conservative unless sings of perforation, sepsis, or persistent bleeding; in such case, gastrectomy is warranted.

Summary

Ischemic gastropathy is highly infrequent in daily medical practice and only very few cases are described in the literature. We present a case of gastroparesis with digestive intolerance and candidemia secondary to gastric ischemia in a 52-year-old neurocritical patient admitted to ICU for a brain hemorrhage. The patient had significant risk factors for gastric hypoperfusion (diabetes mellitus and vasculopathy), which led to secondary gastroparesis with digestive intolerance. Mechanical obstruction and vascular compromise were ruled out in the complementary imaging findings. Consequently, the administration of parenteral nutrition for several weeks was the main risk factor for developing invasive candidiasis.

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The Best Clinical Cases in Respiratory Medicine

Contents

Principles and Management of ARDS

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Contents

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Learning Objectives

- To diagnose ARDS.
- To know what Ventilation-induced lung injury is and how to reduce its risk.
- To be aware of the current knowledge and uncertainties on protective mechanical ventilation.
- To be aware of the adjunctive therapies used in ARDS.
- To know indications and basics of VV-ECMO.

18.1 ARDS Definition, Causes, and Risk Factors

18.1.1 ARDS Definition

The acute respiratory distress syndrome (ARDS) was formally described for the first time in 1967 [1] as a disease characterized by a rapid impairment of gas exchange in adult patients with different underlying primary diagnosis.

The clinical definition of ARDS evolved since then and is today represented by the Berlin definition, which was published in 2013 [2] as the result consensus of the ARDS Definition Task Force, a panel of experts convened in 2011 for an initiative of the European Society of Intensive Care Medicine and endorsed by the American Thoracic Society and the Society of Critical Care Medicine. The Berlin criteria for ARDS replaced the American-European consensus conference (AECC) definition, which was published almost twenty years before, in 1994.

This new definition of ARDS requires the coexistence of 4 conditions, based on etiology, gas exchange, origin of edema, and imaging. To be defined as ARDS, a patient must have (1) a sudden (within 7 days from a known clinical insult or new or worsening respiratory symptoms), (2) impairment of oxygenation (PaO_2/FiO_2 (P/F) < 300 mmHg with a minimum level of 5 cmH_2O of positive end-expiratory pressure) with the evidence of (3) bilateral opacities at lung imaging (CT scan or chest X-ray), and (4) excluding fluid overload or cardiac failure as possible causes of respiratory failure [2].

Despite the advantage of easily diagnosing ARDS at the bedside, the Berlin definition has some controversial aspects (like the difficult diagnosis in monolateral forms or of severe patients undergoing non-invasive ventilation) which were amplified by the recent COVID-19 pandemic.

18.1.2 ARDS Risk Factors

A genetic susceptibility to ARDS is suggested by the association of many genetic variants with ARDS risk. Nevertheless, a clear link between each specific genetic polymorphism and ARDS seems small [3]. ARDS develops after a given event that can affect the lung directly (primary—or pulmonary—ARDS) or many other organs (secondary—or extrapulmonary ARDS).

The main causes of primary ARDS are pneumonia (bacterial or viral), chest injury, inhalation (vomit, smoke, or toxic chemicals), and drowning (*see* ▶ Chap. 20). Secondary ARDS is mainly caused by sepsis, with other possible causes being for example pancreatitis and blood transfusion (transfusion-related acute lung injury, TRALI). Modern causes of ARDS are also e-cigarette or vaping product use (e-cigarette vaping associated lung injury, EVALI). Finally, several cases of ARDS in the postpartum period have also been reported in patients affected by COVID-19 pneumonia (*see* ▶ Chap. 22).

18.1.3 ARDS Classification

Despite the different ARDS etiologies (primary vs secondary) being characterized by certain radiological and mechanical behavior, to date there is no specific clinical role for this classification and is mostly used for didactic purposes. A new approach to further subclassify ARDS patients has focused on inflammatory markers. Calfee et al. described two different ARDS phenotypes (namely hypo-inflammatory and hyperinflammatory) based on the latent class analysis in 2014 [4]. The description of these phenotypes started a discussion on the heterogeneous effects of different treatments suggested for ARDS, such as steroids and immunomodulatory drugs.

18.1.4 Diagnosis and Imaging

As there is no single laboratory test useful to diagnose it, ARDS is defined according to the Berlin definition criteria. Although classical ARDS diagnosis is based on X-ray imaging, lung CT scan may also be used to diagnose ARDS, with the advantage of possibly quantifying lung edema, the amount of collapsed lung tissue, and evaluating recruitability.

Moreover, lung CT scan can identify alterations such as pleural effusion, nodules, or masses, which can be (mis)interpreted as infiltrates on chest X-ray. In the last few years, lung ultrasound has also been suggested to diagnose and/or monitor patients with confirmed or suspected ARDS. Lung ultrasound has been proposed as an alternative to chest radiography for resource-limited settings in the Kigali modification to the Berlin definition of ARDS. The limitations of lung ultrasound include the user expertise required, the high number of artifacts in obese patients, and the impossibility to distinguish hydrostatic pulmonary edema from ARDS. The latter may be overcome by an extended ultrasound evaluation also involving the heart to identify signs of cardiac dysfunction.

18.1.5 Pathophysiology

The general pathophysiological progression and the sequelae of different pathological events characterizing ARDS may be slightly different for the various etiologies of ARDS. For example, ARDS following COVID-19 pneumonia has been shown to predominantly affect the vascular part of the alveoli.

In general, the initial response to injury, also called the exudative phase, is characterized by an innate immune cell-mediated damage of the alveolar endothelial and epithelial barriers and by the accumulation of protein-rich edema within the interstitium and alveoli. The alveolar macrophages already in the lung secrete proinflammatory cytokines, leading to neutrophil and monocyte/macrophage recruitment, as well as activation of alveolar epithelial cells and effector T cells, to promote and sustain inflammation and tissue injury.

The endothelial activation and microvascular injury also contribute to barrier disruption which is worsened by mechanical stretch. The repair processes that start during the second (or proliferative) phase of ARDS are essential for survival. Once epithelial integrity has been reestablished, alveolar edema is reabsorbed, and the provisional matrix restores alveolar architecture and function. The final, or fibrotic, phase of ARDS is not always present but has been linked to an increased time on mechanical ventilation and mortality [5].

18.2 General Management

18.2.1 Mechanical Ventilation

The aim of mechanical ventilation is to guarantee tissue oxygenation, adequate elimination of CO_2, relieve the excessive burden on respiratory muscles, contribute to alveolar stability, and allow therapeutic measures.

Despite being of paramount importance in the treatment of ARDS, mechanical ventilation itself can contribute to the progression of lung damage, defined as ventilator-induced lung injury (VILI). VILI can neither be diagnosed at the bedside nor easily distinguished from ARDS as there is no specific circulating or mechanical biomarker available. To date, it can only be prevented by avoiding known mechanisms of harm, such as high tidal volume, high plateau pressure, and so, most recently, high mechanical power [6].

The acknowledgment of VILI changed the priorities in mechanical ventilation from the complete restoration of gas exchange to the achievement of lung protection with acceptable oxygenation and carbon dioxide (CO_2) removal. Despite the concept of lung protection being now universally accepted and pursued, many aspects of how to obtain this aim are still debated. This can be related to the heterogeneity of patients enrolled in the different clinical trials, the mechanisms of VILI still to be elucidated and to the difficulties of ARDS diagnosis.

Respiratory system compliance (Crs = tidal volume/driving pressure) is generally reduced in ARDS for two reasons. First, the flooding of airspaces with edema, inflammatory cells, and debris reduces the alveoli available for ventilation. Second, the tidal volume is distributed to less alveoli which leads to additional elastic strain.

Indeed, in the early phase of ARDS, which is characterized by hydrostatic edema, the gravitational force determines a distribution of edema through the gravitational axis and a large proportion of tissue (up to 50%) may be airless at the end-expiration. Moreover, the damage to alveolar cell type 2 leads to a reduction in surfactant production, increases surface tension, alveolar flooding, small airways closure, and atel-

ectasis. Ventilating a patient with ARDS may therefore be challenging and the ideal ventilation regimen with minimal risk of VILI is yet to be determined.

18.2.2 Tidal Volume and Plateau Pressure—Volutrauma & Barotrauma

The main goal of mechanical ventilation in the early 70s was to maintain normal $PaCO_2$ levels. To obtain this, high minute volume, especially with high tidal volumes (>10–15 mL/kg), was used, leading to high incidences of *barotrauma* among ARDS patients. After the first experimental evidences of Barotrauma [7], the question whether pressure was dangerous *per se* or if the damage was related to higher tidal volumes (the so called *Volutrauma)* led to the study by Dreyfuss et al. [8], in which different combinations of pressures and volumes were explored. The authors found that animals ventilated with higher volumes but low pressure had the highest incidence of lung trauma. Nevertheless, the final word in the volume/pressure dilemma is yet to be spoken and both parameters are probably interconnected in the concept of transpulmonary pressure. The Dreyfuss experiment, indeed, created high volumes/low pressure by applying negative ventilation, which would be associated with low airway pressure but high transpulmonary pressures. Moreover, the trials assessing protective volumes (low volume) were usually associated with a plateau pressure (Pplat) limit, making it impossible, at the end, to differentiate between the cumulative effects.

In 2000, the ARMA trial [9], which was coordinated by the NIH-NHLBI ARDS Network, a research network formed to study the treatment of acute respiratory distress syndrome, randomized patients to receive two different ventilation protocols: (1) a tidal volume of 12 mL/kg of predicted body weight (PBW) and Pplat targeted to 50 cmH_2O (control group) or (2) a tidal volume of 6 mL/kg PBW and a Pplat targeted to a maximum of 30 cmH_2O (intervention group).

The trial found a significant difference in mortality between the two groups and soon determined a new standard in tidal volume and plateau pressure management in ARDS. This trial was innovative for several reasons, and mainly because it changed the vision of mechanical ventilation from a way of restoring gas exchange to a tool to provide acceptable oxygen delivery/CO_2 removal while aiming for lung protection.

Recent studies are focusing on the role of ultra-low tidal volume ventilation (i.e., <6 mL/kg of PBW), especially during extracorporeal carbon dioxide removal or ECMO (NCT04832789, NCT04349618), but until now no strong evidence exists about an additional benefit, as compared to standard (6 mL/kg) low tidal volume ventilation strategy.

18.2.3 Positive End-Expiratory Pressure—Atelectrauma

The concept of positive end-expiratory pressure (PEEP) in ARDS was first introduced in the same paper that firstly described ARDS [1]. Patients ventilated with a continuous (and not intermittent) positive pressure were found, indeed, to be less prone to atelectasis and to have a higher oxygenation.

PEEP can counteract the high tendency of ARDS lungs to collapse, caused by the interstitial edema and therefore by the pressure superimposed on the dorsal lung by increasing intra-alveolar pressure. For these reasons, PEEP quite soon became a standard of care in ARDS patients. Despite the possible benefits of PEEP on alveolar collapse and oxygenation, the debate today is focused on how much PEEP we should use in ARDS patients.

Although some parts of the lung may be "recruited", and therefore reopened, following the application of a certain positive level of PEEP, this does not account for the entire airless parenchyma. Consolidated and flooded lungs will not be opened (and therefore recruited) even with higher pressures. The recruitable lung is therefore the one characterized by hydrostatic interstitial edema which determines the alveolar collapse due to an increase of the superimposed pressure which then overcomes the alveolar pressure. Setting an adequate level of PEEP can thus be useful in ARDS to avoid tidal recruitment/derecruitment—and therefore reduce atelectrauma—and to increase oxygenation.

Nevertheless, since pressure distribution within the lung is not homogeneous, the increase of pressure determined by the increase of end-expiratory pressure may determine overinflation in some other parts of the lung, classically considered to be positioned in the least gravity-dependent region (ventral lung in patients in supine position) or at the interfaces between closed and open regions. This phenomenon may cause *per se* injury and the two phenomena—*i.e.* benefit of recruitment and injury on overinflated regions—may coexist. Setting PEEP in this context may be challenging, also because these phenomena are different among patients and in the same patient at different times. Monitoring is necessary to personalize PEEP levels in order to reduce the risk of lung damage.

Many different techniques of lung monitoring have been suggested to personalize PEEP. Since PEEP is usually used in ARDS patients to improve oxygenation, which can also be achieved by increasing FiO_2, the ALVEOLI [10] study compared two different strategies of ventilation: (1) low PEEP/high FiO_2 and (2) high PEEP/low FiO_2. None of the two strategies demonstrated to be superior to the other, and this can be related to the fact that oxygenation per se (namely SpO_2, which was the target of the trial) may not be the best aim to assess the overall effect of a protective strategy of mechanical ventilation. The PEEP/FIO_2 tables introduced in the study are still clinically used today and can be considered one of the simplest ways to personalize PEEP in mechanically ventilated ARDS patients.

Another way of personalizing PEEP derives from the physiology of ARDS and is evaluating the pressure–volume (P/V) relationship [11] of the respiratory system, aiming at setting a PEEP above the lower inflection point. However, CT scan and EIT-based studies demonstrated that the P/V curve of the respiratory system may not be representative of the entire parenchyma, underestimating or overestimating pressure targets of different lung regions. Moreover, current evidence suggests that the lower inflection point found in the P/V curve may, in some cases, represent the opening of the main airway—and not alveolar reopening.

Another breakthrough in PEEP setting was associated with the evidence of driving pressure as the major determinant of mortality in ARDS [12]. Since its introduction, strategies aiming at achieving the lowest driving pressure have been used

worldwide, despite the original study only finding an association, and not a causation, between driving pressure and mortality. Studies investigating the direct effect of driving pressure on mortality in ARDS are still warranted.

Some advanced monitoring techniques, like esophageal pressure monitoring and electrical impedance tomography (EIT), may be helpful to personalize PEEP to avoid overinflation and collapse. Both techniques allow investigating the regional heterogeneity of lung inflation and may therefore be useful bedside to reduce the risk of VILI.

Despite a first monocentric trial investigating the use of esophageal pressure (Peso) to optimize PEEP (EPVent1) showed positive signals in terms of mortality reduction in ARDS, a second multicenter randomized clinical trial (EPVent2) designed to overcome the limitations of the first one showed negative results. Secondary analysis of the same study revealed that in some subpopulations, the use of Peso to set PEEP can be favorable [13].

To date, no big RCT has evaluated the effects of EIT-guided PEEP setting on a patient's outcome. EIT provides several parameters potentially useful for optimizing PEEP (e.g., center of ventilation, dorsal fraction of ventilation, number of hyperinflated areas, relative percentage of overinflated, and collapsed pixels). Despite this, none of these parameters has been demonstrated to improve outcomes when used to optimize PEEP. More recently, EIT also offers the possibility to evaluate regional ventilation/perfusion mismatch which has been associated with the worst outcome in ARDS patients. If targeting V/Q mismatch using PEEP and vasoactive drugs can improve outcome is still to be explored.

18.2.4 Spontaneous Breathing in ARDS—P-SILI

If the patients are not treated with neuromuscular blocking agents and are able to use the respiratory muscles to a variable extent, this can also contribute to the development of lung damage by increasing transpulmonary pressure. This may happen before (e.g., when the patient is spontaneously breathing with enriched oxygen devices or during noninvasive ventilation (NIV)) or after intubation, when the patient is in assisted ventilatory mode. The negative pressure created by the respiratory muscles can lead to high transpulmonary pressures and therefore expose the patients to a risk of lung damage. This damage driven by the patient's effort has been defined as patient self inflicted lung injury (P-SILI) [14].

Vigorous spontaneous breathing in animal models of ARDS showed to increase lung injury despite limiting both plateau pressure and tidal volume. This may be related to the increase of transpulmonary pressures, caused by the high negative pressures generated by the respiratory muscles. Furthermore, despite no systematic trial has been conducted to evaluate the impact of high efforts on ARDS outcome, individual case reports showed a correlation between strong inspiratory efforts and the occurrence of lung injury, namely lung oedema/barotrauma or oxygenation worsening.

Today, the risk of P-SILI represents the root of discussion about the use of NIV in ARDS or about spontaneous breathing during the weaning phase. The use

of higher PEEP during spontaneous breathing may indeed expose the patient to a higher risk of barotrauma, despite the recent ROSE trial suggests that patients treated with higher PEEP can have safe spontaneous breathing under light sedation [15].

To date, a definitive net balance between the risk of P-SILI and the alternative risks that may come from endotracheal intubation or prolonged deep sedation and muscle relaxant infusion has not been defined yet and a personalized treatment approach should be followed.

18.2.5 Prone Positioning

Prone position (PP) has been used for a long time as rescue therapy for severe hypoxemia in patients with ARDS because of its beneficial effect on oxygenation. Moreover, PP has been extensively used during the COVID-19 pandemic and despite the main reason for putting a patient in PP is the effect on hypoxemia, the benefits of PP are not limited only to an improvement in oxygenation. PP can reduce the risk of ventilator induced lung injury (VILI) by improving stress/strain distribution. It has also been shown to reduce the concentration of pulmonary proinflammatory cytokines and can homogenize aeration and ventilation distribution throughout the lung. For all these reasons, PP may also effectively impact a patient's outcome by reducing VILI.

The protective effect of PP and oxygenation improvement are probably unmatched since conflicting results on the association between oxygenation response and mortality have been found. Current guidelines suggest using prone positioning in severely ill ARDS patients (P/F < 150 mmHg). The PROSEVA study [16], done in 27 ICUs, showed a significant reduction in mortality in ARDS patients included after a 12- to 24-h stabilization period with a PaO_2/FIO_2 ratio <150 mmHg associated with PEEP of at least 5 cmH_2O, an FIO_2 of at least 60%, and tidal volume of 6 mL/kg PBW. In the PROSEVA trial, the PP group had 4 sessions of 17 consecutive hours (the protocol planned sessions of at least 16 h) on average and PP was continued even in the absence of improved oxygenation.

During the COVID-19 pandemic, prone positioning has been widely used both in invasively ventilated and spontaneously breathing patients. Due to the delayed effect of PP in some patients and the limited resources available, a strategy of prolonged prone position (>16 h) was proposed [17]. In COVID-19 patients, prolonging PP seems to be beneficial in terms of survival and may therefore represent the next major step forward in Iung protective mechanical ventilation. The exact mechanism of improved survival in prolonged prone positioned patients and the generalizability to other non-COVID-19 ARDS must be still explored.

18.2.6 Pharmacological Therapy

There is no specific pharmacological therapy for ARDS. The treatment is therefore based on managing the underlying cause and on supportive therapy. Several drugs have been tested for their possible role in the pathogenetic chain of ARDS. Of the many drugs tested it is worth citing:

- *Corticosteroids:* the use of corticosteroids in ARDS is theoretically justified by the activation of inflammatory pathways and the recruitment of monocytes and neutrophils in the lung tissue. They have been used in ARDS due to their anti-inflammatory and antifibrotic properties.

  Several guidelines address the use of steroid therapy in ARDS. The Surviving Sepsis Campaign's COVID-19 guidelines include a weak recommendation for corticosteroids in patients with COVID-19 and ARDS. Given the lack of strong evidence for the use of steroid therapy in patients with ARDS, it is perhaps not surprising that only one in five patients with ARDS receives steroid therapy [18].

  The uncertainty about the use of corticosteroids for ARDS is based mainly on the possible side effects of the steroid therapy, including hyperglycemia, infections, weakness, gastrointestinal bleeding, and delirium. Although steroid therapy may not be useful in all ARDS patients, some hyperinflammatory subgroups (or "phenotypes") may find higher benefit from their use [4].
- *Pulmonary vasodilators*: Hypoxia is determined by an increase of ventilation/perfusion (V/Q) mismatch, and in ARDS this is classically translated in an increase of shunt and low V/Q areas. The improvement of gas exchange is always associated with an improvement of V/Q mismatch. One way to manipulate V/Q is the titration of mechanical ventilation, but in some cases, neither PEEP, tidal volume, nor FiO_2 allow for an adequate improvement of V/Q mismatch.

  In these cases, the manipulation of V/Q may be done by shifting the circulation from hypoventilated areas (which usually are in the dependent lung, near the shunt areas) to normally or hyperventilated ones. V/Q will then be more matching and gas exchange may improve. One way of shifting perfusion may be the use of inhaled nitric oxide (iNO), a potent vasodilator recommended to treat pulmonary hypertension in newborns. Although the use of iNO in ARDS is physiologically justified, it has not shown definitive effects on mortality, and therefore is not suggested in all ARDS patients. Moreover, its use may be associated with kidney injury. Inhaled epoprostenol has been suggested as an alternative to iNO since it may reduce potential side effects, is easier to administer, and has lower costs.
- *Sedation, analgesia, and neuromuscular blockers:* Sedatives and opioids are usually administered to invasively ventilated patients to reduce pain and anxiety, increase safety and comfort, and to minimize the risk of agitation and delirium. Moreover, the use of neuromuscular blockers is also common in ARDS patients to improve oxygenation and reduce the risk of barotrauma. However, their use has not been associated with a decrease in mortality, ventilator-free days, or the duration of MV.

  Although deep sedation and paralysis may be necessary in the first hours after intubation, prolonged infusion of high doses of sedatives and muscle relaxants may increase the risk of delirium, muscular weakness, and therefore contribute to prolonged weaning.

  For these reasons, new strategies of light sedation, aiming at having a collaborating awake patient, and early short-term muscle relaxant infusion may be appropriate to exploit the full benefit (see Delirium, in *Complications of ARDS*) [19].

18.3 Extracorporeal Membrane Oxygenation (ECMO)

Extracorporeal membrane oxygenation (ECMO) is a temporarily supportive strategy that aims at maintaining acceptable oxygenation and CO_2 elimination buying time while injured lungs recover from the underlying disease. Unlike invasive mechanical ventilation, ECMO is ideally free from risk of VILI. At the same time, several severe complications (e.g., bleeding and thrombosis) characterize the use of ECMO and as such have limited its use. Recent advances in technology have reduced ECMO complexity and increased its safety, which has led to increased use and improved outcomes. However, the positive effects on patients' outcome are not supported yet by sufficient scientific evidence to make ECMO a strongly recommended strategy for the treatment of moderate to severe ARDS.

During ECMO, a pump drives blood flow through the extra corporeal circuit, which includes an oxygenator and a sweep-gas flow which, respectively, enable blood oxygenation and gas exchange. Veno-venous ECMO (VV-ECMO) is the strategy most frequently applied in severe ARDS. In VV-ECMO venous blood is drained from the right atrium via a large vein (e.g., the internal jugular or femoral vein) and returned oxygenated and with low CO_2 content to the right atrium. A more recent and minimally invasive ECMO technique, named extracorporeal CO_2 removal ($ECCO_2R$), facilitates the so-called "(ultra)lung protective ventilation" reducing the risk of VILI. However, $ECCO_2R$ does not provide oxygenation support.

18.3.1 Indications

When evaluating the possibility of initiating VV-ECMO in a patient with severe ARDS, it is of high importance to take the cause of the respiratory failure into consideration. ECMO in ARDS will be possible only if the injury is considered reversible, refractory to conventional treatments, and the patient does not present formal contraindications for the initiation of ECMO. The only exception with possible initiation of ECMO despite irreversible disease is bridge to lung transplant.

$ECCO_2R$ may be used to facilitate ultraprotective strategies of mechanical ventilation in moderate to severe ARDS. Possible criteria for initiating $ECCO_2R$ are a pH lower than 7.25 for more than 2 h together with a plateau pressure lower than 28 cmH_2O for more than 2 h [20].

VV-ECMO is used as rescue therapy in patients with severe ARDS and refractory life-threatening hypoxemia and/or hypercapnia or patients that have a transpulmonary pressure too high and, as such, are at high risk for VILI. Although clinical trials have used different cutoffs for recruiting patients, following the (Extracorporeal Life Support Organization) ELSO guideline 2021 [21], the initiation of VV-ECMO can be considered when at least one of the following criteria is fulfilled:

1. PaO_2/FiO_2 ratio lower than 80 mmHg, despite optimal medical management, including a trial of prone positioning.
2. Hypercapnia with pH < 7.25, despite optimal conventional mechanical ventilation with respiratory rate lower than 35/min and plateau pressure lower than 30 cmH_2O.
3. bridge to lung transplantation.

In this assessment, the RESP score for ECMO survival prediction and the Murray Scores for estimating the mortality if ECMO is not initiated are useful.

18.3.2 Contraindications

Relative contraindications for ECMO are (1) cerebral hemorrhage; (2) significant and/or irreversible central nervous system (CNS) injury; (3) systemic bleeding; (4) contraindications for anticoagulation; (5) immunosuppression; (6) older age, although there is no specific threshold for age; and (7) mechanical ventilation for more than 7 days with plateau pressure > 30 cmH_2O and FiO_2 > 90%.

18.3.3 Management

- Anticoagulation

  Patients on ECMO need systemic anticoagulation to prevent thrombotic complications. The anticoagulation strategy that is most often used in patients on ECMO is continuous infusion of unfractionated heparin. The target of anticoagulation can vary according to different variables (e.g., the set extracorporeal blood flow, the ECMO technique used, and other concomitant patient-related risk factors promoting coagulopathies). The level of induced anticoagulation can be monitored using different variables such as activated partial thromboplastin time and activated clotting time. In case of heparin-induced thrombocytopenia, alternative anticoagulants, as direct factor Xa inhibitors or thrombin inhibitors, are used.
- Hb ≥ 10 g/dL

  The ELSO guidelines recommend keeping Hb higher than 10 g/dL (>12 g/dL) to optimize tissue oxygenation during ECLS. Practice is, however, highly variable among centers and more studies are needed to reach a consensus.
- (Ultra)lung protective ventilation

  Ventilator settings should be chosen to limit VILI. However, the optimal ventilatory strategy for ARDS patients on ECMO is unclear. Ideally, severely injured lungs should not undergo any mechanical stress or strain. However, whether further reducing tidal volume and/or plateau pressure would improve patients' survival needs to be addressed and no studies or guidelines indicate specific limits. For instance, the use of a high or low positive end-expiratory pressure is still controversial. Controlled mechanical ventilation is the ventilatory strategy of choice often applied in this patient population. After the acute phase of the illness, assisted ventilation may be considered because it might improve diaphragmatic function and reduce need for sedation. At the same time, assisted ventilation may expose the patients to P-SILI and asynchronies. Further studies are needed to investigate the best ventilatory modes during ECMO.
- *Sedation*

  Patients on ECMO do not need to be sedated *per se*, but the need for sedation often derives from the severity of the underlying disease. During recovery and weaning from ECMO patients can be without any sedation provided they are cooperative as dislocation of the cannulas represents an often-fatal emergency.

- *Laboratory parameters*

  While on ECMO, haptoglobin, lactate dehydrogenase, and D-Dimers should be assessed daily. In these patients, it is important to evaluate and monitor hemolysis as the ECMO circuit represents a foreign extracorporeal circuit with which the patient's blood is in constant contact.

  Several studies strongly suggest that referral of patients to centers with proven ECMO expertise improves patients' outcome [22]. Transfer to experienced centers should happen as soon as possible.

18.4 Complications of ARDS

Patients affected by ARDS may have several complications, deriving from the undergoing disease or related to the prolonged ventilatory treatment. Among them:

- *Barotrauma:* Barotrauma can affect ARDS patients both in the beginning (early) or in the last phase (late complication) of the disease. ARDS is a risk factor for pulmonary barotrauma, due to the physical stress of positive pressure mechanical ventilation on acutely damaged alveolar membranes. The incidence of barotrauma in ARDS is about 10%. Pulmonary barotrauma from invasive mechanical ventilation refers to alveolar rupture due to elevated trans-alveolar pressure (the alveolar pressure minus the pressure in the adjacent interstitial space). Air leaks into extra-alveolar tissue can determine conditions like pneumothorax, pneumomediastinum, pneumoperitoneum, and subcutaneous emphysema. Keeping low pressures (both plateau and peak pressures) and low volumes can limit the occurrence of barotrauma. Persistent air leak via chest thoracostomy in mechanically ventilated patients may indicate the presence of parenchymal discontinuity, such as an alveolo-pleural or broncho-pleural fistula. These conditions require prompt diagnosis and treatment and may prolong the weaning process (*see* ▶ Chap. 23).
- *Ventilator-associated pneumonia (VAP)*: VAP is defined as pneumonia developing ≥48 h after endotracheal intubation. Hospital-acquired (or nosocomial) pneumonia (HAP) and ventilator-associated pneumonia (VAP) are important causes of morbidity and mortality despite improved antimicrobial therapy, supportive care, and prevention. Being intubated for ARDS increases the risk of VAP.
- *Delirium:* Delirium is defined as an acute brain dysfunction and occurs in up to 80% of the Intensive Care Unit (ICU) population. Critically ill patients are subject to numerous risk factors for delirium. Some of these, such as exposure to sedative and analgesic medications, may be modified to reduce the risk of delirium. ARDS is associated with a greater risk for ICU delirium than mechanical ventilation *per se*, and the association between ARDS and in-hospital mortality is weakened after adjusting for delirium and coma. A recent multicenter study on COVID-19 ARDS patients found an incidence of delirium of more than 50% [23], with benzodiazepine use and lack of family visits being the most modifiable risk factors for delirium.

  Current evidence suggests that a light sedation protocol, with analgesia target first and a minimization of sedation, can reduce delirium, provide early rehabilitation, and ICU discharge [19]. Nevertheless, this strategy may be difficult to be applied in ARDS patients, since deep sedation and/or paralysis is often required.

A way to prevent excessive and inappropriate sedation in ARDS may be a prompt recognition of preventable discomfort factors, such as pain, anxiety, or patient-ventilator asynchrony. The immediate recognition of asynchronies and the adaptation of ventilator settings (e.g., use of pressure mode, spontaneous breathing, inspiratory trigger, and appropriate PEEP level) should be considered before administering additional sedatives to avoid potentially unnecessary deep sedation and/or paralysis.

- *Poor nutrition and muscle weakness*: increased breathing exercise, hypoxia and prolonged sedation may increase the risk of muscle wasting and weakness. The type of ventilation, and specifically controlled mechanical ventilation, has been linked to an increased risk of diaphragmatic dysfunction and therefore may reduce the chances of quick liberation from mechanical ventilation *(*see also ▶ Chap. 25).

Take-Home Messages

- ARDS is a complex and heterogeneous syndrome, and its diagnosis is currently based on the Berlin criteria, despite a discussion is ongoing on the update of the definition.
- Mechanical ventilation is fundamental in ARDS patients but can cause lung damage. Current evidence suggests the use of low tidal volumes, low plateau pressure, and prone positioning in severe ARDS patients. PEEP setting is still debated, but the one associated with the lowest risk of both atelectrauma and barotrauma may be preferable.
- Lung monitoring is essential in understanding the heterogeneity of lung mechanics in ARDS patients. Using advanced respiratory monitoring, like esophageal catheters and/or electrical impedance tomography, may help individualizing respiratory treatment and reducing the risk of VILI
- Spontaneous breathing in ARDS patients must be allowed under tight surveillance; inappropriate high inspiratory effort can increase lung and muscle damage.
- When mechanical ventilation is not capable of achieving good protective and gas exchange target, alternative options must be considered like prone positioning, VV-ECMO, vasodilators, and corticosteroids.

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Near Drowning in Seawater: A Case Report

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Contents

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Learning Objectives

- Pathophysiology of near drowning.
- General management of a nearly drowned patient.
- The "ten actions to prevent drowning" suggested in the Global Report on Drowning.

19.1 Introduction

Drowning was first defined in 2002 by the World Congress of Drowning as respiratory impairment due to immersion or submersion in a liquid medium. Drowning is a public health issue responsible for 360,000 deaths each year worldwide, being one of the ten major causes of death among children and young people. Children under 5 years are the most at risk for drowning and more than half of the victims are below 25 years of age [1]. Contact of hyperosmolar seawater with alveoli generates a series of damages such as alteration of pulmonary surfactant and rupture of cell membranes with inflammation and generation of alveolar edema, leading to a condition very similar to acute respiratory distress syndrome [2]. Drowning often requires mechanical ventilation and Intensive Care Unit management. However, among nearly drowned patients, nearly 30% show criteria of acute respiratory distress syndrome [2] usually with a fast recovery, and lung sequelae are rare [3]. To date, there are no specific guidelines for managing and treating nearly drowned patients, being the management of these patients mainly based on acute respiratory distress syndrome guidelines [2] and personal on-field experience [4]. The aim of this case report is to describe the management and treatment from first aid to Intensive Care Unit discharge of a nearly drowned young patient who developed acute respiratory distress syndrome.

Case Presentation

We present the case of an 18-year-old Afro-American male (height 190 cm, weight 80 kg, BMI 22,2 kg/m^2) rescued from seawater close to the rocks of the Ligurian region in the city of Genoa. He was spending some free time with friends when, after a dive, something went wrong. The bystanders referred that they picked him up close to the water unconscious, and they began basic life support immediately, achieving a return of spontaneous circulation after cardiac arrest. At the emergency team's arrival, the Glasgow coma scale was 3/15, and the first monitored peripheric saturation of oxygen was around 20%. After a few minutes of advanced cardiovascular resuscitation (using a fraction of inspired oxygen of 100% administered via manual bag-mask ventilation), the patient was awake but agitated, peripheric saturation of oxygen was 80%, and oro-tracheal intubation, with a rapid sequence induction, was performed. The patient was connected to a mechanical ventilator and hemodynamically monitored, including continuous electrocardiography. The patient's past medical history was empty. The patient was transferred to the Emergency Department of the hub-referring hospital for receiving advanced critical care and properly treating the upcoming acute respiratory failure.

19.2 Investigations

19.2.1 Emergency Department

Neurologic status and investigations. The patient arrived at the Emergency Department deeply sedated, paralyzed with neuromuscular blocking agents, and invasively ventilated. The neurologic clinical examination was not repeated. The cerebral computed tomography scan showed no acute bleeding nor density alterations or midline shift. Skull bones were intact. The spine computed tomography scan was normal with no evidence of fracture.

Pulmonary investigations and gas exchange. At the point-of-care ultrasound exam, diffused lung B-lines and gastrectasia were found. Chest computed tomography scan showed total thickening with air bronchogram in both inferior lobes of the lungs, coherent with drowning. In the ventilated parenchyma, signs of ground-glass thickening suspicious of acute respiratory distress syndrome were reported (see Fig. 19.1). The abdominal computed tomography scan reported periportal edema but no signs of organ lesions. The first arterial blood gas analysis reported a mild acute respiratory acidosis and severe respiratory insufficiency: pHa 7.23, arterial oxygen tension 86.7 mmHg, arterial carbon dioxide tension 48.5 mmHg, arterial partial pressure of oxygen/fraction of inspired oxygen ratio 96. Hemoglobin 133 g/L, glycemia 118 mg/dL, sodium 147 mmol/L, potassium 3.2 mmol/L, Ionized calcium 1.28 mmol/L, serum lactate 3.5 mmol/L, and bicarbonate 20.5 mmol/L.

Hemodynamic monitoring. Advanced hemodynamic monitoring was installed with an invasive catheter for arterial pressure and continuous heart rate monitoring, a venous central catheter, and a continuous electrocardiogram. Electrocardiogram reported a sinus rhythm and normal electrical activity.

Blood investigations. The following blood investigations were performed: biochemical tests, complete coagulation, blood cell count, toxicology, and severe acute respiratory syndrome coronavirus-2 swab (tested negative).

Other monitoring and investigations. The body temperature was assessed with periodic measurements using an external thermometer. The urinary output was assessed every hour with a urinary catheter.

19.2.2 Intensive Care Unit

Neurologic status and investigations. During the Intensive Care Unit course, the patient's neurological status was investigated every 6 h.

Pulmonary investigations and gas exchange. The first chest X-ray was performed after the first cycle of prone positioning lasting more than 12 h, it showed bilateral opacity in the interstitial-alveolar space. The second chest X-ray was performed 1 h after extubation, it reported a normal aspect of both lungs. Additionally, a total of two bronchoscopies were performed; the first, 12 h after Intensive Care Unit admission, was triggered by severely impaired gas exchange: it showed normal bronchial mucosa and few bronchial secretions, microbial samples were collected; the second

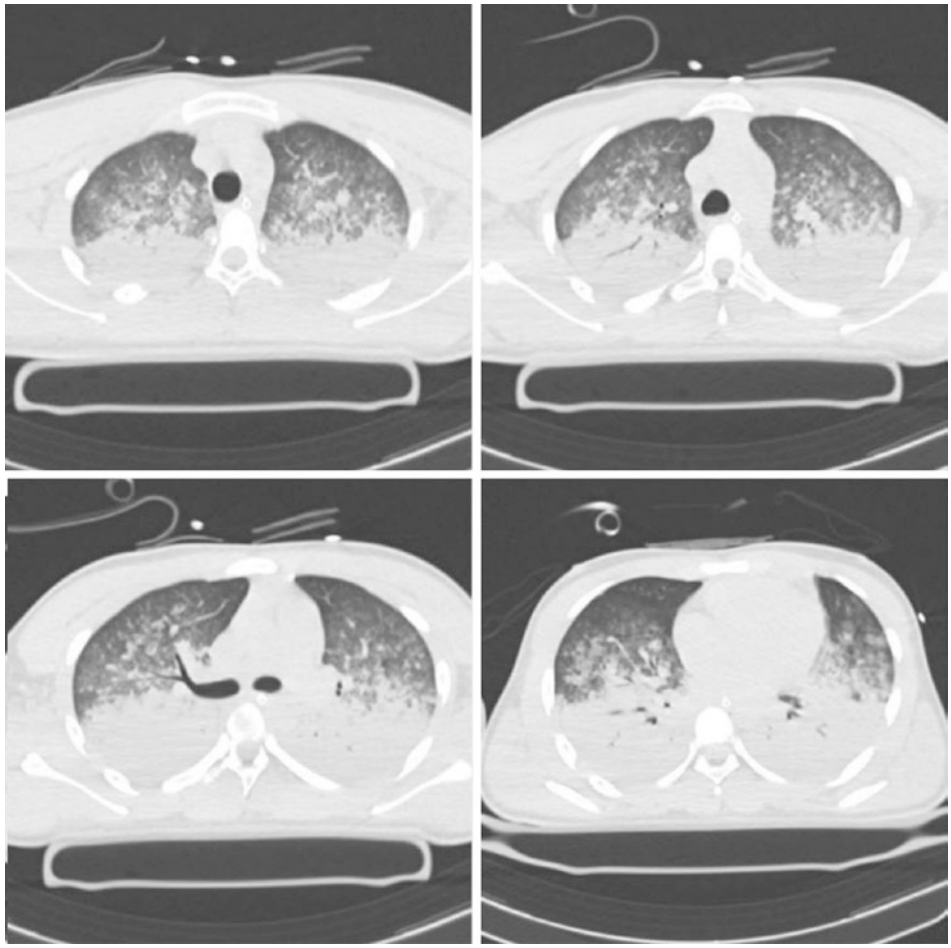

Fig. 19.1 Thoracic computed tomography: ground glass pattern in the ventilated lungs region. Thickening in the basal regions of both lungs

bronchoscopy was performed 24 h after Intensive Care Unit admission because of the need for high pressure ventilation (plateau pressure 30 cmH_2O and driving pressure 20 cmH_2O). It revealed inflamed bronchial mucosa, especially in the left lung, with the presence of few but deeply stuck bronchial secretions.

Hemodynamic monitoring. Hemodynamic parameters were monitored continuously. Fluid balance was assessed every 6 h.

Blood investigations. Blood analytic exams were assessed daily. Microbial investigations: bronchoalveolar lavage cultures were all negative, *Candida auris* swab was negative, and *Klebsiella pneumoniae* swab was negative. Human immunodeficiency virus, Hepatitis B virus, and Hepatitis C virus were all negative.

Other monitoring and investigations. The body temperature was assessed continuously with an axillary temperature probe. Urinary output was assessed with a urinary catheter and urinometer every hour.

19.3 Differential Diagnosis

Near drowning, polytrauma, cerebrovascular accident, cardiovascular accident, intoxication. Based on the results of blood exams and the thoracic computed tomography, all the differential diagnoses were excluded apart from near drowning.

19.4 Treatment

19.4.1 Emergency Department

Neurologic management. The patient arrived at the emergency department sedated, oro-tracheally intubated, paralyzed with neuromuscular blocking agents, invasively mechanically ventilated, and fully monitored for neurologic, hemodynamic, respiratory, and metabolic parameters.

Pulmonary management. Given the B-lines at point-of-care ultrasonography and altered gas exchange, a first lung recruitment was performed. Invasive mechanical ventilation was set up with the following parameters: volume controlled ventilation, tidal volume 6.6 mL/kg of predicted body weight, positive end-expiratory pressure 14 cmH_2O, respiratory rate 18/min, and fraction of inspired oxygen 90%. Following the results of arterial blood gas analysis and thoracic computed tomography scan and given the inability to improve the gas exchange using protective invasive mechanical ventilation, the patient underwent rescue manoeuvers and was placed in the prone position (within 1-h from the hospital admission). Also, a recruitment manoeuver was repeated, and mechanical ventilation was set at the following parameters: pressure controlled ventilation, inspiratory pressure 15 cmH_2O, positive end-expiratory pressure 20 cmH_2O, respiratory rate 20/min, inspiratory /expiratory ratio 1:1 and fraction of inspired oxygen 90%. Positive end-expiratory pressure was assessed by choosing the value that guaranteed the most protective ventilation and the best gas exchange, without impairing hemodynamic.

Hemodynamic and hemo-coagulative treatments. The hemodynamic parameters were stable with a mean arterial pressure of 88 mmHg and a rhythmic heart rate of 77 bpm, without adrenergic or vasoactive drugs. Intravenous crystalloids were administered. The laboratory exams were within normal range and without indication for blood or plasma transfusion or reversal of coagulation.

Other treatments. A gastric tube was placed. A total of 2000 mL of clear fluids were drained from the stomach during the emergency department stay. Body temperature was 33 °C, and active rewarming was started. Spontaneous urine output was 3.5 mL/kg/h of clear urine in the absence of diuretics.

19.4.2 Intensive Care Unit

The patient was admitted to theIntensive Care Unit, sedated, paralyzed, and mechanically ventilated. At the arrival, body temperature was 33.1 °C but was increased via active warming, mean arterial pressure was 65 mmHg but returned to normal values without vasoactive drugs. At Intensive Care Unit admission, the patient was placed

in the prone position, and the first arterial blood gas analysis reported a severe respiratory acidosis and respiratory insufficiency with an arterial partial pressure of oxygen/fraction of inspired oxygen 98.7 (pH 7.10, arterial partial pressure of carbon dioxide 88.9 mmHg, bicarbonate 21 mmol/L); ventilatory support was modified with augmentation of the respiratory rate up to 24/min followed by an improvement of respiratory acidosis (pHa 7.28, arterial partial pressure of carbon dioxide 63 mmHg), but arterial partial pressure of oxygen/fraction of inspired oxygen ratio remained at 92. A broad-spectrum empiric antimicrobial therapy with linezolid (600 mg q12 h) and piperacillin/tazobactam (18 g/225 mg continuous infusion q24 h) was started at admission and then adapted under infectiology's indication as follows: ceftobiprole 500 mg q8 h + metronidazole 500 mg q8 h. Steroidal therapy was started with intravenous methylprednisolone 1 mg/kg ideal body weight (80 mg q24 h). Minimal enteral feeding was started within the first 12 h (6.25 kcal/kg/day).

During the first days of the Intensive Care Unit course, the patient was maintained sedated (using propofol continuous infusion), paralyzed (using neuromuscular blocking agents continuous infusion), and with continuous analgesia (fentanyl intravenous continuous infusion). Body temperature was normal, hemodynamics were stable, and adrenergic or vasoactive drugs were not necessary. A diuretic stimulus was maintained for the first 36 h and gradually reduced after return of spontaneous urinary output.

Invasive mechanical ventilation was maintained for 2 days. The patient underwent two cycles of prone positioning, each one lasting 12 h and a total of 32 h of continuous infusion of neuromuscular blocking agents. Mechanical ventilation parameters were modified to maintain a protective setting. After the second cycle of prone positioning, the arterial blood gas analysis improved significantly: pHa 7.53, arterial partial pressure of carbon dioxide 31.1 mmHg, arterial partial pressure of oxygen/fraction of inspired oxygen 425; continuous infusion of neuromuscular blocking agents was stopped, and mechanical ventilation was gradually adapted until return of spontaneous breathing. Sixteen hours after the interruption of curarization, the patient was ventilated with pressure support ventilation (pressure support 14 mcH_2O, positive end-expiratory pressure 7 cmH_2O, fraction of inspired oxygen 35%, and spontaneous respiratory rate of 10/min). The arterial blood gas analysis showed: pHa 7.37, arterial partial pressure of oxygen 116 mmHg, arterial partial pressure of carbon dioxide 51.5 mmHg, arterial partial pressure of oxygen/fraction of inspired oxygen 332.

19.5 Evolution, Outcome, and Follow-up

Analgesia and sedation were gradually reduced, and the patient promptly awake, executing simple orders, movements and strength were preserved. After extubation the patient did not show any neurological deficits. One hour after the extubation, the patient was spontaneously breathing room air, the arterial blood gas analysis confirmed sufficient gas exchange: pHa 7.38, partial pressure of carbon dioxide 46.6 mmHg, arterial partial pressure of oxygen/fraction of inspired oxygen 304. Enteral feeding was stopped before extubation, as well as parenteral nutrition (22 kcal/kg/day) and the patient rapidly returned to spontaneous oral intake. Strictly periodical arterial blood gas analyses were performed after extubation (Fig. 19.2)

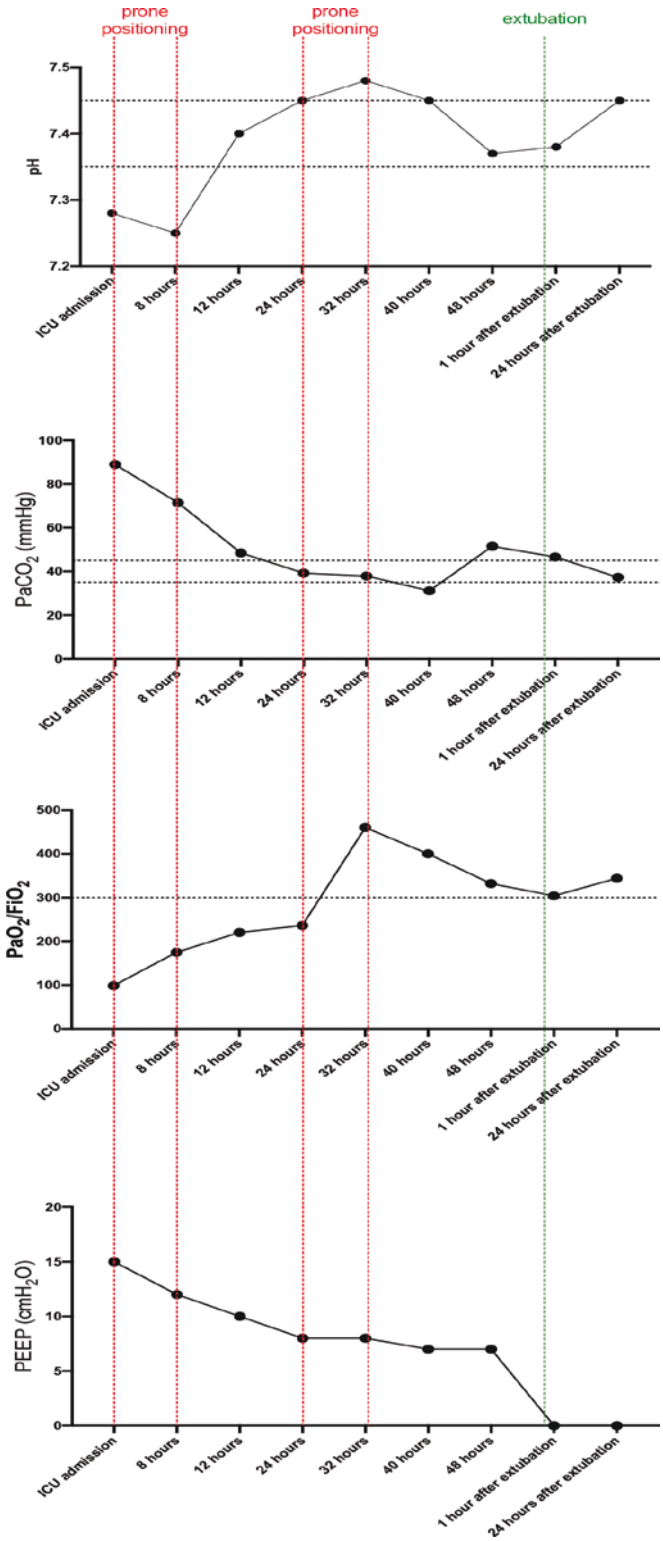

Fig. 19.2 Arterial blood gas analysis and ventilation parameters: trends of the principal parameters of the arterial blood gas analysis and of the invasive mechanical ventilation monitored during the treatment. pH (normal values 7.35–7.45), $PaCO_2$ carbon dioxide tension (normal values 35–45 mmHg), PaO_2/FiO_2 arterial partial pressure of oxygen/fraction of inspired oxygen (normal values > 300). PEEP positive end expiratory pressure (normal values > 5 cmH_2O)

with progressive improvement of gas exchange. A few hours after extubation, the patient confirmed the diagnosis of accidental near drowning; he did not realize he was unable to swim. Twenty-four hours after extubation, the patient was discharged to the ward where antimicrobial therapy was ended on day 5 together with de-escalation of steroidal therapy. The patient showed an increase in blood transaminases and, due to the suspicion of an infectious trigger, further examinations in an outpatient setting were planned. The patient was discharged from the hospital 10 days after admission.

19.6 Discussion

This clinical case wants to discuss near drowning in a young patient in seawater who was clinically and radiologically diagnosed with acute respiratory distress syndrome and treated accordingly. Acute respiratory failure is an immediate consequence of near drowning and the treatment is oriented around the prevention of complications [4]. The initial management of a (nearly) drowned unconscious subject who is not spontaneously breathing should be oriented in giving advanced cardiac support and respiratory support to improve oxygenation and prevent cardiac arrest [5]. In this clinical case, all those steps were followed. The patient was resuscitated by a trained eyewitness until achieving return of spontaneous circulation. The emergency team rapidly performed advanced life support, and the patient arrived at the hospital intubated, invasively mechanically ventilated, and hemodynamically monitored. According to the literature, nearly drowned patients should undergo several examinations to assess respiratory function and imaging diagnostic tests. Blood tests are needed to evaluate renal and liver function, electrolytes, and potential toxins [3]. Our investigations showed severe lung impairment compatible with acute respiratory distress syndrome due to near drowning.

There is no strong evidence to support the treatments of this condition, as it emerges from the literature [4], ventilation should be set with a lung-protective approach. Positive end-expiratory pressure should be titrated up to a value where oxygenation improves significantly. In our patient, rescue therapies such as recruitment manoeuvers and prone positioning were performed with the aim to re-open the collapsed alveoli and improve gas exchange, minimizing the pressures applied to the lungs. In this patient, weaning from mechanical ventilation was started when the patient was considered ready to be extubated according to a positive spontaneous breathing trial. Antibiotic and steroid therapies should not be started as prophylaxis [3–5]. However, the incidence of ventilator-associated pneumonia is increased in nearly drowned ventilated patients [3], so we decided to start antibiotics and steroids [4] due to a suspected pulmonary infection.

Submersion duration was identified as a strong predictor for good outcome [6], especially when below 5 min. In our case, we cannot report the duration of submersion but according to the patient's neurological outcome, it is suspicious of a submersion below 5 min. In addition to the prompt initiation of basic life support, the rapid

response of the emergency system positively impacted on the patient's outcome [6]. Lastly, the World Health Organization global report on drowning [1] reiterates the call for the prevention of drowning as the most powerful tool to face this issue graved by the fact that victim's outcome is often poor and the invitation to know the "10-actions to prevent drowning".

Take-Home Messages

- Near drowning is a not addressed as worldwide issue that results in numerous deaths each year.
- Near drowning is a rare disease with some peculiarities which should be known by the clinicians who face this clinical entity.
- Acute respiratory distress syndrome pattern is often present at the beginning, but recovery is faster and lung sequelae are rare.
- Further investigations leading to evidence-based treatments and specific guidelines are needed.

Summary

(Near) drowning is characterized by the immersion or submersion in a liquid medium which becomes responsible for the damage seen in the lungs; the contact of the hyperosmolar seawater with the alveoli generates alveolar edema and a radiological and clinical condition very similar to acute respiratory distress syndrome. Initial advanced cardiorespiratory management plays a pivotal role on patient outcome. Nearly drowned patients may present with acute respiratory failure: during the first minutes, it is fundamental to ensure adequate ventilation and oxygenation including invasive mechanical ventilation. After stabilization, patients should undergo clinical, radiological, and laboratory examinations to evaluate respiratory function and potential accompanying injuries. Respiratory failure should be managed with protective mechanical ventilation including rescue strategies (i.e., prone positioning), if necessary. Antibiotic and steroidal therapy should not be used as prophylaxis. Despite some similarities with acute respiratory distress syndrome, patients usually recover quickly, and lung sequelae are rare. The most relevant predictor of a good outcome is the duration of submersion, especially when below 5 min; rapid intervention of the emergency systems positively impacts the outcome. In the last global report on drowning, the World Health Organization identified (near) drowning as a worldwide not addressed issue that is responsible for many people's deaths, especially among young people. Prevention of drowning is fundamental and is the most important tool to limit the number of victims. Sharing clinical experience and the results of treatments are fundamental to establish dedicated guidelines.

Acknowledgments We acknowledge the healthcare staff who cared for the patient.

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The Use of Inhaled Nitric Oxide for Acute Respiratory Distress Syndrome in a Patient with a Subarachnoid Hemorrhage. A Clinical Case

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Contents

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Learning Objectives

- How to manage the complex interactions between acute brain and lung injury.
- The use of iNO as a treatment for severe hypoxemia in the setting of acute brain injury.
- Beneficial effects of iNO in preventing secondary brain damage in patients with SAH.

20.1 Introduction

Subarachnoid hemorrhage (SAH) is responsible for 6–8% of all acute cerebrovascular events, 5% of deaths, and 25% of the potential life years lost. The development of an acute respiratory distress syndrome (ARDS) in the setting of acute brain injury (ABI), such as SAH, is not an uncommon clinical setting. The management plan for ARDS can be challenging in this setting and treatment for both pathologies may be in opposition. Protective ventilator strategies in ARDS may require permissive hypercapnia and rescue therapies such as prone position to improve oxygenation, whereas ABI is managed with normocapnia or hypocapnia and prone position could mean increased intracranial pressure (ICP). Moreover, respiratory dysfunction may compromise adequate oxygen delivery to the brain and may lead to secondary brain damage and a worse outcome. INO is a selective pulmonary vasodilator that decreases pulmonary resistance and improves ventilation-perfusion matching and oxygenation in patients with pulmonary hypertension or ARDS and could be a successful therapy in these clinical settings. The use of inhaled nitric oxide in ARDS is not uncommon, but its use in ABI has so far not been established. Here we report a clinical case of a patient with severe SAH with increased intracranial pressure and ARDS secondary to aspiration pneumonia, refractory to conventional treatment that successfully responded to the use of iNO.

Case Presentation

A 63-year-old female patient, with a personal history of arterial hypertension and dyslipidemia, was admitted to the Emergency Department (ED) of a peripheral hospital due to acute onset of intense headache accompanied by presyncope symptoms and nausea. She described the headache as the worst she had ever experienced. She arrived with a systolic blood pressure (SBP) of 150 mmHg, heart rate (HR) of 65 bpm, chest auscultation was clear, and had a normal respiratory rate with peripheral oxygen saturation (SpO_2) of 96% at ambient air. Later, she presented sudden deterioration in the level of consciousness, with a Glasgow Coma Scale (GCS) of 4 associated to decerebrate posturing and anisocoria with left mydriasis. Rapid sequence intubation was performed followed by a CT scan that showed a SAH (Hunt & Hess grade IV, WFNS grade V, and Fisher grade 4) with a right subdural hematoma, secondary to the rupture of a saccular aneurysm in the supraclinoid segment of the right carotid artery (Fig. 20.1). With these findings, the patient was transferred to our tertiary hospital, where she underwent an emergency craniotomy (clipping the aneurysm

and evacuating the subdural hematoma) and multimodal neuromonitoring was placed (intracranial pressure (ICP) and partial brain tissue oxygenation ($PtiO_2$) sensors). After neurosurgery, she was admitted to our Intensive Care Unit (ICU). Treatment with Nimodipine 60 mg/4 h po was started as well as analgesia and sedation to maintain ICP < 20 mmHg and cerebral perfusion pressure (CPP) >60 mmHg. She was connected to a mechanical ventilator under volume-controlled ventilation (VCV) with a PEEP of 8 cm of H_2O and FiO_2 0.5 with adequate oxygenation and ventilation parameters. Hemodynamics were stable with MAP 75 mmHg. Post-surgical CT scan showed right frontotemporal post-surgical changes with practical stability of the known subarachnoid hematic content, as well as presence of diffuse brain swelling with decreased displacement of the midline shift of 5-6 mm. The angiographic study showed the presence of correct exclusion of the aneurysm (Fig. 20.2). The second day after admission, the patient presented progressive hypoxemia and a chest X-ray showed bilateral condensations (Fig. 20.3), requiring deep sedation as well as neuromuscular blockade with Cisatracurium at 0.3 mg/kg/min intravenously (iv). With a suspected diagnosis of ARDS secondary to an aspiration pneumonia, cultures of respiratory samples were taken and empirical antibiotherapy with Amoxicillin-Clavulanic acid 2 g/8 h iv was started. Respiratory cultures were positive for *Hafnia alvei* and *Stenotrophomonas maltophilia* so antimicrobial therapy was changed to Cotrimoxazole 160/800 mg/8 h iv and Cefotaxime 2 g/8 h iv. Severe hypoxemia persisted in spite of the established treatment.

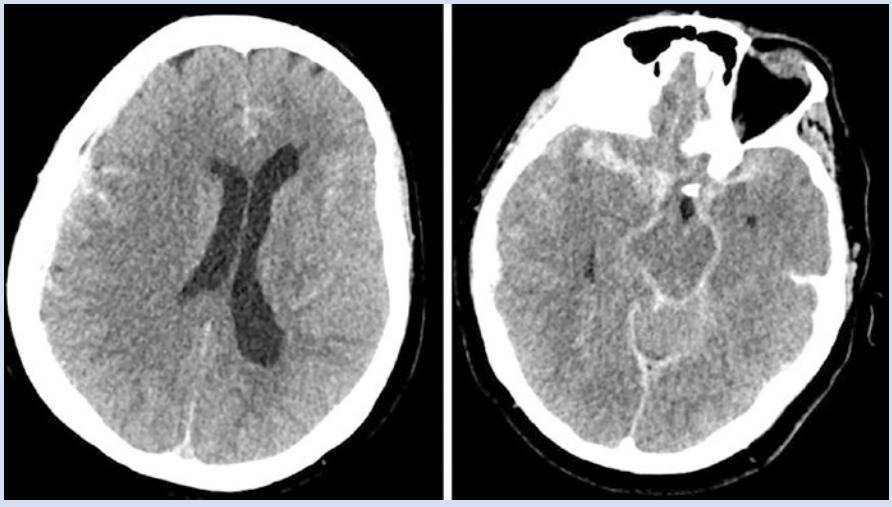

Fig. 20.1 Preoperative CT scan (day 1)

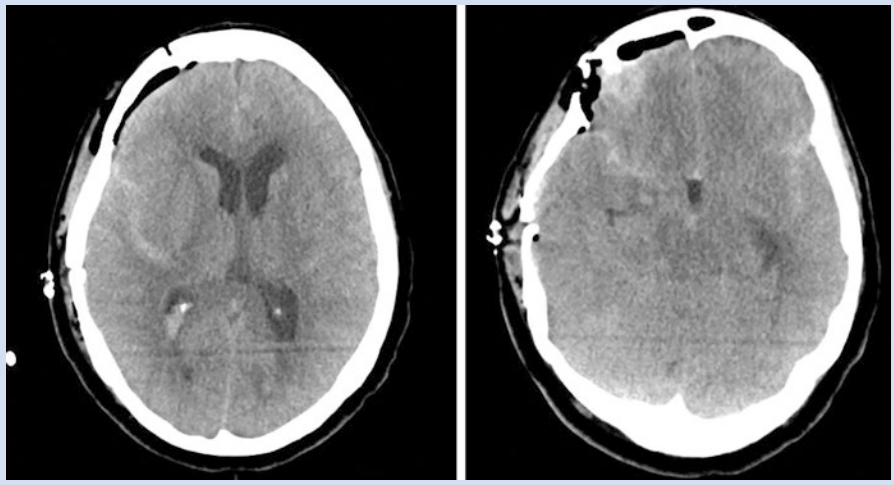

Fig. 20.2 Post-surgical CT scan (day 1)

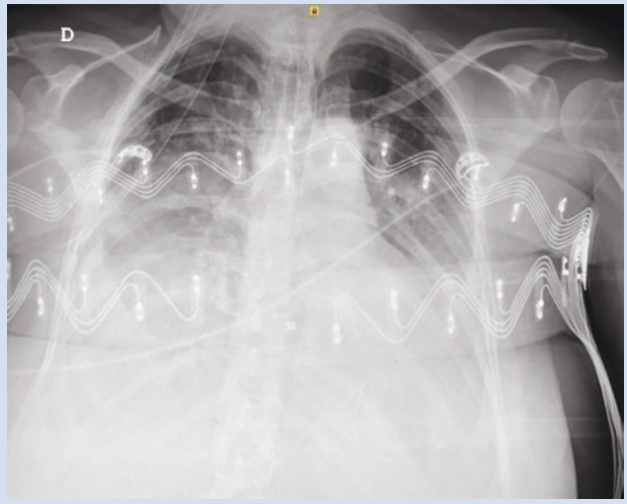

Fig. 20.3 Chest X-ray on day +2 (before iNO)

20.2 Investigations

Figures and investigations attached in the last section.

20.3 Differential Diagnosis

ARDS secondary to aspiration pneumonia was our initial clinical suspicion, but other causes of hypoxemia had to be taken into account. Neurogenic pulmonary edema (NPE) is an increase in pulmonary interstitial and alveolar fluid that is due to an acute central nervous system injury that usually develops rapidly after the injury and could be a plausible differential diagnosis in this setting. In this case, given the presence of positive respiratory cultures, it appears that the worsening is related to a respiratory infection. Other causes as cardiogenic pulmonary edema, pulmonary hemorrhage should be considered but are less probable in this case.

20.4 Treatment

Despite adequate antibiotic treatment and lung protective ventilation (CMV FiO_2 1.0, PEEP 8 cm H_2O, Vt 6 mL/kg (65 kg ideal body weight), respiratory rate 20 pm), severe hypoxemia persisted. Arterial blood gas analysis showed pH 7.31, $PaCO_2$ 46 mmHg, and PaO_2 67 mmHg (PaO_2/FiO_2 ratio 67). Electrical impedance tomography (EIT) and esophageal pressure balloon were placed to monitor and optimize mechanical ventilation parameters. The patient did not respond to increasing PEEP and recruitment manoeuvers. A prone manoeuver was performed with poor neurological tolerance (ICP > 25 mmHg and $PTIO_2$ < 15) with reduction of CPP from 65 to 45 requiring emergent supine positioning and treatment with 20% mannitol iv. At this point, iNO was started to improve pulmonary mismatching. iNO was started with 15 ppm, then gradually increased up to 20 ppm. Within the next 12–24 h, PaO_2 and $PaCO_2$ improved, with blood gas analyses as follows: pH 7.43, $PaCO_2$ 32 mmHg, and PaO_2 134 mmHg. FiO_2 was reduced from 1.0 to 0.65, PEEP maintained in 8 cmH_2O and chest X-ray evidenced reduction of bilateral condensations (◘ Fig. 20.4). ICP also showed gradual improvement from 20 to 5 cm H_2O with an improvement of CPP. Norepinephrine was needed during 24 h for keeping mean arterial pressure (MAP) above 90 mmHg.

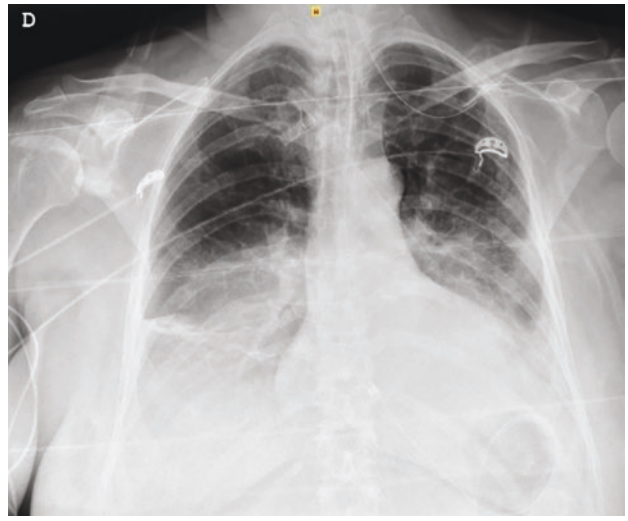

Fig. 20.4 Chest X-ray on day +5 (after 72 h of starting iNO)

20.5 Evolution, Outcome and Follow-up

iNO was discontinued after 1 week of treatment and the patient remained stable. She was tracheostomized on the tenth day of admission because of a critical illness myopathy and weaned from the ventilator on day 30th. When the sedation was withdrawn, the patient was conscious with a GCS of 15 and a mild left hemiparesis, with no other neurological deficit. On day 38th after admission, the patient presented an episode of altered consciousness. We performed a cranial CT scan showing acute hydrocephalus, and a ventriculoperitoneal shunt was placed. After the procedure, she recovered to her previous neurological condition, and a control CT showed reversal of the hydrocephalus. Further stay in the ICU remained uneventful, and she was transferred to the referral hospital on day 45th. Patient remained in hospital for 3 months doing neurological rehabilitation and then was discharged.

20.6 Discussion

Among extracerebral organ failure, respiratory dysfunction is the most common complication in severe ABI. This can lead to secondary brain injury due to hypoxemia. The management of raised ICP includes adequate oxygenation as well as normocapnia and trying to keep the CPP at 60–70 mmHg. Additional actions are raising the head up to 30–45° and maintaining the head in an adequate position to optimize venous return. On the contrary, in patients with severe ARDS, permissive hypercapnia may be required, as well as prone manoeuver in patients not responding to conventional treatment. iNO is increasingly used in ICUs for patients with ARDS because of its potent vasodilatory effect exclusive on pulmonary vasculature, but its use in acute brain injury is not yet clear [1–3].

In the present clinical case, the administration of iNO at 20 ppm led to an improvement of both oxygenation and cerebral hemodynamics. This beneficial effect of iNO in patients with acute brain and lung injuries has been suggested in multiple small clinical studies, but randomized controlled clinical trials are needed to validate it [1, 3–5]. In each case, the addition of iNO to the conventional treatment modalities allowed a rapid improvement of arterial oxygenation and a decrease of ICP. iNO is a potent vasodilator, but it is generally admitted that iNO is promptly inactivated in the bloodstream, leading to an almost exclusive effect on pulmonary vasculature, without major effects on systemic blood pressures. In patients suffering from ARDS, iNO has been shown to selectively dilate blood vessels only in those lung segments that are actively participating in gas exchange at the alveolar capillary level, improving ventilation-perfusion matching [1]. Regarding its effects on the brain NO plays a significant role in a variety of neurobiological processes, and treatment with iNO could also have extrapulmonary effects. Several beneficial functions of NO have been identified in the nervous system, mediating and protecting neuronal activity, and could be involved in host-defense mechanisms. There is growing evidence of NO involvement in various pathophysiological mechanisms underlying neuronal disorders, so a potential cytotoxic effect in high concentrations should be considered [6]. In patients with SAH, endogenous NO concentrations are significantly reduced because of dysfunction of the endothelial NO-synthase and numerous other pathomechanisms. This local NO deficit is thought to be related to the early microcirculatory dysfunction in experimental and clinical SAH. NO depletion is also thought to contribute to post-hemorrhagic microthrombosis formation and inflammatory changes which further aggravate brain damage and post-hemorrhagic ischemia after SAH, so administration of iNO may reduce secondary brain damage [4, 5]. Another study in 7 patients showed that administration of iNO in SAH patients is safe, with no adverse events necessitating the cessation of iNO [5].

In conclusion, there is a potential benefit of iNO in patients combining subarachnoid hemorrhage and ARDS, with little or none adverse effects and more studies are needed to validate and aupport its clinical use.

Take-Home Messages

- It is important to know the brain–lung interactions.
- Patients with acute brain injury can develop respiratory failure requiring additional therapeutic actions.
- There is a potential benefit of INO in patients with subarachnoid hemorrhage and ARDS with severe hypoxemia. To date, no major adverse effects on brain physiology have been found.

Summary

A 63-year-old female patient was admitted to the ICU after an aneurysmal subarachnoid hemorrhage requiring emergency craniotomy. In the first 48 h after admission, the patient developed an ARDS secondary to an aspiration pneumonia, with positive respiratory cultures for *Hafnia alvei* and *Stenotrophomonas maltophilia.* Severe hypoxemia did not respond to antibiotic therapy, profound sedation, neuromuscular blockade or increasing PEEP and recruitment manoeu-

vers. Ventilation in the prone position was not tolerated because of an increase in intracranial pressure (ICP 25 > mmHg) and low cerebral perfusion pressure. Treatment with iNO was started, allowing a rapid and sustained improvement of both arterial oxygenation and cerebral hemodynamics. iNO was discontinued after 1 week and the patient remained stable. Sedation was progressively withdrawn, the patient was conscious with a mild left hemiparesis and no other neurological deficit. After 45 days she was discharged from the ICU, started neurological rehabilitation, and 3 months later was discharged home.

Acknowledgments To all the team involved in patient's care.

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Postpartum Acute Respiratory Distress Syndrome (ARDS) in a Patient with Suspected Amniotic Fluid Embolism After Complicated Childbirth

L. J. Engelhardt, Oliver Hunsicker, and Jan Adriaan Graw

Contents

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Learning Objectives

- Symptoms of amniotic fluid embolism
- Differential diagnosis and treatment of postpartum ARDS
- Psychological burden of being treated in the ICU after childbirth

21.1 Introduction

Amniotic fluid embolism is a rare but severe peripartum complication that can be life-threatening for the mother and the newborn [1, 2]. The complex pathophysiology is explained by the entrance of amniotic fluid antigens into the maternal circulation leading to an activation of coagulation, mechanical obstruction by thrombotic material, and an uncontrolled immune response, similar to anaphylaxis or septic shock [2]. Complement activation and immune and cytokine storm cause vasoplegia, capillary leak, and subsequent alveolar damage, though the exact pathophysiological mechanisms have yet to be resolved [2]. Clinical symptoms include sudden onset of peripartum respiratory insufficiency, hypotension, cardiac failure, cardiac arrest or arrhythmias, disseminated intravascular coagulation, massive hemorrhage, pulmonary arterial vasoconstriction, ARDS, and multiorgan failure [1–3].

Here we discuss the case of a 33-year-old female patient with postpartum ARDS treated with VV-ECMO and showing major symptoms of amniotic fluid embolism after complicated childbirth. We aim to highlight two relevant topics: Firstly, the clinical presentation and management of postpartum ARDS after suspected amniotic fluid embolism, which is a rare, life-threatening peripartum complication [1, 2]. Secondly, we discuss the psychological burden for the critically ill mother of being treated in the ICU in the vulnerable postpartum phase, where the risk for depression is increased, particularly after complications [4].

Case Presentation

A 33-year-old female patient developed postpartum ARDS and multiorgan failure after complicated childbirth.

According to the reports from the external obstetrics center, the following complications occurred prior to ARDS development and transfer to our center: Vaginal childbirth was complicated due shoulder dystocia. Severe postpartum hemorrhage, symptoms of shock, and a sudden episode with a decrease in peripheral oxygen saturation to 80% were observed after regular delivery of the complete placenta. Uterine dilatation and palpation were performed; no placental remnant was identified. Completely compromised coagulation was described. Blood products (red blood cells, plasma, platelets, fibrinogen, and prothrombin complex concentrate) were transfused. Bleeding management was performed according to the national guidelines on peripartum hemorrhage, diagnosis, and therapy current at that time (S2k Level, AWMF Registry No.015/063, March 2016). After operative bleeding control, a sudden ventricular tachycardia with consecutive cardiac arrest and need for brief cardiopulmonary resuscitation was reported. Subsequently, the patient was

transferred under sedation and mechanical ventilation to the ICU of the external hospital for further hemodynamic stabilization and coagulation management.

In the further course, the local ARDS referral center was contacted due to development of acute respiratory failure with severely compromised oxygenation. At the timepoint of transfer to the ARDS department, the patient was deeply sedated with a Richmond Agitation Sedation Scale of −5. She was mechanically ventilated via an endotracheal tube. Nitric oxide inhalation with 30 parts per million was initiated by the ECMO-retrieval team to reduce pulmonary vascular resistance, improve ventilation/perfusion-mismatch, and achieve transportability. Despite escalation of mechanical ventilator settings (FiO_2 1.0, peak pressure 35 mbar, PEEP 20 mbar, inspiration:expiration proportion 1:1), a tidal volume of only 172 mL and a minute ventilation of 2.2 L/min were achieved. The patient presented with severe ARDS at ICU admission (peripheral oxygen saturation 84%, PaO_2 52.3 mmHg, PCO_2 54.6 mmHg, pH 7.19). Furthermore, the patient was hemodynamically instable in septic shock with inflammatory response symptoms. Tachycardic sinus rhythm >120 bpm and a continuous infusion of norepinephrine at maximum doses of 2.3 µg/kg/min were necessary to achieve a mean arterial pressure of 65 mmHg. In addition, the patient developed acute anuric renal failure.

Medical and family history: The patient suffered from gestational diabetes. The infant, large for gestational age, survived and was transferred and treated in the department of neonatology.

Figure 21.1a illustrates the maternal symptoms observed postpartum in the presented case with suspected amniotic fluid embolism.

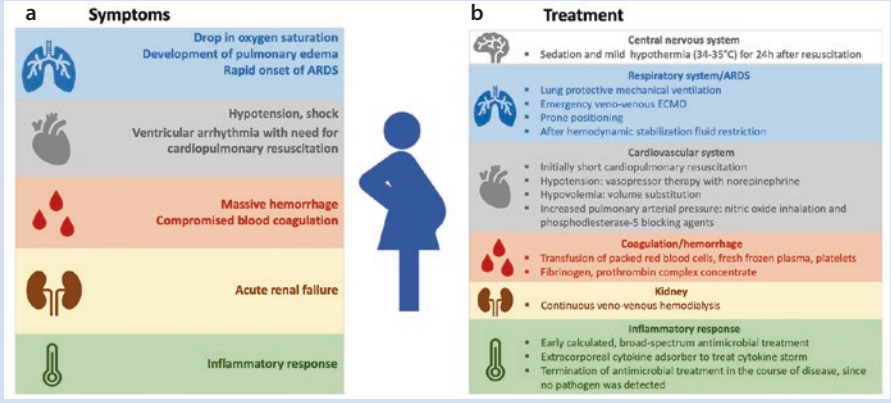

Fig. 21.1 **a** Maternal symptoms observed after complicated childbirth in the presented case with suspected amniotic fluid embolism. **b** Treatment strategies in the presented case with suspected amniotic fluid embolism. Abbreviations: Acute Respiratory distress syndrome (ARDS), Extracorporeal Membrane Oxygenation (ECMO)

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21.2 Investigations

Table 21.1 shows an organ-structured overview of relevant diagnostics performed at ICU admission in the ARDS center. Further diagnostics performed during the course of disease are described in the evolution, outcome, and follow-up section.

Table 21.1 Investigations at the day of ICU admission in the ARDS center

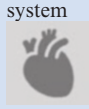
Central nervous system 	*CT (cranial)*: No indication for hypoxic-ischemic encephalopathy early after resuscitation. No indication for hemorrhage or infarction. Medial interhemispheric fissure, symmetrical ventricular system, basal cisterns, and fourth ventricle visible. Investigation of somatosensory evoked potentials and determination of neurone-specific enolase 72 hours after resuscitation were scheduled.
Respiratory system 	*CT (thoracic)*: Complete consolidation of the left lung, partial consolidation of the right upper and lower lobe, and ground-glass opacities of the right upper, middle, and lower lobes suggestive for pneumonia or pulmonary edema. Right-sided pleural effusion (26 mm). No signs for arterial pulmonary embolism as far as the subsegmental plane. No signs for aspirated fluids in the central airways. *Chest X-ray*: Bilateral, confluent pulmonary opacities *Blood gas analysis* before ECMO: PaO_2 41.4 mmHg, PCO_2 61.1 mmHg, pH 7.14, FiO_2 1.0 with PaO_2/FiO_2 ratio (Horovitz index) <100 mmHg (severe ARDS according to Berlin definition) No bacteriological, virological, or mycological pathogens were detected by laboratory analysis in blood, urine, and bronchoalveolar lavage. Autoimmune antibodies were unremarkable.
Cardiovascular system 	*Transthoracic echocardiography*: In the initial orientational echocardiography pericardial effusion was observed which was spontaneously regredient. While left ventricular function was good, right ventricular dysfunction with a tricuspid annular plane systolic excursion of 14 mm via M-mode, and a right ventricular end-diastolic diameter of 41 mm, were observed in the four chamber view. Systolic pulmonary arterial pressure plus central venous pressure was 30 mmHg +20 mmHg = 50 mmHg. *Laboratory*: NT-pro BNP 943 ng/L (normal value <125 ng/L), troponin T 741 ng/L (normal value <14 ng/L)
Coagulation system Immunohematology 	*Laboratory*: Platelets 64 /nL (normal range 150–370 /nL), INR 2.15 (normal range 0.9–1.25), fibrinogen 0.94 g/L (normal range 1.6–4.0), prothrombin time 37% (normal range 70–130%), activated partial thromboplastin time 71 s (normal range 26–40 s), antithrombin III 47% (normal range 80–120%), fibrin degradation product (D-dimer) >20.00 mg/dL (normal value <0.5 mg/L, physiologically elevated in pregnancy). The modified international society on thrombosis and hemostasis scoring system for disseminated intravascular coagulation in pregnancy considers the parameters reduced platelets, prolonged prothrombin time or INR, and reduced fibrinogen. [3] *Transfusion-associated lung injury diagnostics*: Human leukocyte antigen (HLA) antibodies and human neutrophilic granulocyte antibodies in the transfused blood products of donors were negative
Kidney 	*Laboratory*: Creatinine 2.79 mg/dL (normal range 0.5–0.9 mg/dL), urea 59 mg/dL (normal range 17–48 mg/dL), potassium 6.0 mmol/L (normal range 3.5–5.0 mmol/L) *Urinary output*: Anuria

Table 21.1 (continued)

Inflammatory response, microbiology 	*Laboratory*: Procalcitonin 52.2 µ/L (normal value <0.5 µ/L), CRP 28.1 mg/L (normal value <5.0 mg/L), leukocytes within normal range *Microbiology*: Blood cultures, urine, tracheobronchial, bronchoalveolar lavage without pathogen detection until ICU discharge
Abdomen	*CT (abdominal)*: Uterus postpartum enlarged. No signs for active bleeding by contrast-enhanced blood. Pancreatic edema and thickened bowel walls. Perihepatic and perisplenic ascites *Laboratory*: Bilirubin total 2.02 mg/dL (normal value <1.2), ALT 225 U/L (normal value <31 U/L), AST 603 U/L (normal value <35 U/L). *Sonography uterus*: Postpartum well contracted, no signs for intrauterine blood clots, ascites

References of laboratory values are presented in brackets behind the measured value; if multiple values were available, the most pathologic value during day of ICU admission was reported

21.3 Differential Diagnosis

Differential diagnoses for postpartum development of ARDS were as follows:

- Amniotic fluid embolism: Considered as the most probable diagnosis according to the reported history of sudden onset after complicated childbirth and the combination of symptoms including hypotension, massive hemorrhage, compromised coagulation, respiratory failure, cardiac arrest, and a severe immune response.
- Transfusion-associated lung injury: Differential diagnosis of transfusion-associated lung injury was unlikely as indicated by immunohematologic investigation of human leukocyte antigen (HLA) antibodies and human neutrophilic granulocyte antibodies in the transfused blood products of donors, which were negative.
- Aspiration: Macro-aspiration was neither observed, nor reported by the intubating team or after bronchoscopy. In addition, there were no radiological findings in chest radiographs or thoracic CT scans that were suggestive for an aspiration of fluids into the central airways.
- Infectious cause/pneumonia: No infectious symptoms prior to admission in the external obstetric center were reported. The missing detection of pathogens in microbiologic specimens also supported a non-infectious cause. In addition, early broad-spectrum antimicrobial therapy was applied. The rapid onset of ARDS after childbirth was very likely connected to complications during childbirth.

21.4 Treatment

Central nervous system: The patient initially remained deeply sedated. According to the post-resuscitation standards at the time of the case, targeted temperature management with mild hypothermia (34–35 °C) was induced for 24 hours after ventricular tachycardia and resuscitation.

Respiratory system: At ICU admission, pulmonary gas exchange was deteriorating despite further escalation of mechanical ventilation and adjustment of nitric oxide dose. Due to the massive pulmonary edema, very high peak inspiratory pressures were required. Decision for immediate emergency VV-ECMO by bifemoral cannulation was made, outflow cannula 23 Fr/38 cm right, and inflow cannula 17 Fr/50 cm left. The initial ECMO blood flow was 3.5 L/min and sweep gas flow 2.5 L/min. Lung protective mechanical ventilation and fluid restrictive therapy were commenced once the VV-ECMO circuit was established and the patient showed initial signs of cardiopulmonary stabilization. A first period of prone positioning for 16 hours was performed.

Cardiovascular system: The patient stabilized after volume substitution, transfusion of red blood cells, and administration of coagulation products (see below). Weaning of catecholamine therapy was possible. Subsequently, fluid restrictive therapy and negative fluid balance were started. Increased pulmonary artery pressure was treated with phosphodiesterase-5 blocking agents in addition to therapy with inhaled nitric oxide. There was no need for treatment of the initially detected pericardial effusion because it receded spontaneously.

Coagulation system: After further administration of fresh frozen plasma, fibrinogen, and prothrombin complex concentrates, coagulation stabilized.

Abdomen: No further obstetric interventions were necessary to control the bleeding. Observed ascites was treated conservatively. Liver enzymes increased in the first days after ICU admission. Enteral nutrition therapy via nasogastric tube was started on the first day after ICU admission. Glucose values at ICU admission were mild hypoglycemic; intravenous glucose was applied.

Kidney: Acute renal failure with anuria was treated with continuous veno-venous hemodialysis.

Inflammation and microbiology: Calculated antimicrobial treatment with piperacillin/tazobactam was applied after specimen for microbial diagnostics was extracted. An extracorporeal cytokine adsorber was added to hemodialysis to treat cytokine storm.

Figure 21.1b presents treatment strategies performed in this patient with suspected amniotic fluid embolism.

21.5 Evolution, Outcome, and Follow-Up

Fortunately, the patient stabilized and started to recover from organ dysfunction.

Central nervous system and psychosocial aspects: Neurophysiologic investigation showed somatosensory evoked potentials without pathologic signs. Neurone-specific enolase 72 hours after resuscitation was 62.9 μg/L (reference value <16.3 μg/L). After reduction of sedation on day 3 after admission, the patient presented with movement of all extremities at first awakening. Patient's wakefulness and awareness increased in

the following course. However, later on, the patient developed depressive symptoms and sleep disturbances. The psychiatrist consult service was involved and recommended mirtazapine therapy. The mother's first-born, school-aged child visited early during ICU stay with support of the social service. The newborn child was treated in the department for neonatology for several days. The first bonding between infant and mother was performed lately during ICU stay.

Respiratory system: The respiratory situation improved following ARDS management with VV-ECMO, inhaled nitric oxide, and prone positioning. Overall, three periods of prone positioning (16 hours each) on VV-ECMO with intervals of supine position were performed. Chest X-ray 4 days after ICU admission showed considerably regressive bilateral pulmonary infiltrates. VV-ECMO was successfully weaned after 5 days of treatment. Weaning from mechanical ventilation was successfully performed after dilatative tracheotomy. Spontaneous breathing was firstly achieved on day 6 and high-flow therapy started on day 11 after ICU admission. At timepoint of transferal to a weaning center, the patient was breathing spontaneously, with phases of intermittent nasal high-flow oxygen therapy and continuous positive airway pressure (CPAP) therapy.

Cardiovascular system: Vasopressor therapy with norepinephrine was finally terminated on ICU day 9. At ICU discharge, transthoracic echocardiography showed no signs for regional wall motion abnormalities; left ventricular ejection fraction was 60% without signs for diastolic dysfunction. There was a normal right ventricular function and minor aortic valve insufficiency; mitral-, pulmonal-, and tricuspid valve were morphologically and functionally normal without signs for insufficiency. Pericardial effusion receded completely.

Coagulation: During the 20-day ICU course in our ARDS center, the patient received an overall of 12 units of packed red blood cells, 20 units of fresh frozen plasma, and 6 units of platelet concentrates. In addition, fibrinogen and prothrombin complex concentrates were administered.

Therapeutic anticoagulation during VV-ECMO treatment was performed by activated partial thromboplastin time (PTT)-driven continuous administration of unfractionated heparin. Anticoagulation with unfractionated heparin was initially continued in a prophylactic dose after VV-ECMO weaning and subsequently changed to prophylactic low molecular weight heparin.

Abdomen and nutrition: Liver enzymes decreased in the further course. Nutrition was performed enterally via a nasogastric feeding tube. In the course of the disease, normoglycemia was spontaneously achieved without the need for insulin therapy. Dysphagia assessment and training was performed by logopedics with consecutive initiation of oral feeding.

Kidney: Kidney function started to improve with slightly increasing urinary output, while retention parameters were still increased. Intermittent hemodialysis every 4 days was still necessary at ICU discharge.

Inflammation and Infection: Inflammatory parameters further increased in the early period of the acute phase of critical illness, and calculated antimicrobial therapy with piperacillin/tazobactam was supplemented with ciprofloxacin. However, no pathogen was detected in the diagnostic material extracted prior to initiation of antibiotic treatment. In the late period of the acute phase of critical illness, inflammatory parameters were regredient. Antimicrobial treatment was deescalated and finally terminated. At the timepoint of discharge from our ICU, inflammatory parameters were low.

Mobilization level: The woman frequently received physiotherapy and was mobilized to the sitting position in the chair. After 20 days of treatment in the ARDS center, the patient was transferred to another ICU in our department and some days later to a weaning center.

21.6 Discussion

Regarding the reported history of complicated childbirth and the symptoms, we considered amniotic fluid embolism as the most probable diagnosis for the life-threatening postpartum period with multiorgan failure including severe ARDS. The patient fulfilled the criteria for typical amniotic fluid embolism. This included sudden onset of hypotension, respiratory compromise, massive hemorrhage, coagulation parameters indicative for disseminated intravascular coagulation, clinical onset within 30 min of delivery of the placenta, and absence of confounding explanations for the symptoms [1, 3]. However, coagulation parameters were not measured prior to blood loss. Diagnostic criteria should be reported in future data analysis for clear definition of amniotic fluid embolism and improved comparability of outcomes. So far, no gold standard confirmatory diagnostic test for amniotic fluid embolism is available [1, 3].

Severe inflammatory response was observed in the presented patient. Alveolar damage in amniotic fluid embolism may be explained by the immune response and cytokine storm with capillary leak [2]. Gestational diabetes was reported in the presented case and recently in 12.2% of patients with amniotic fluid embolism [1]. In this patient, postpartum ARDS was successfully managed with VV-ECMO. In a previous analysis of postpartum ARDS, mean PaO_2/FiO_2 before ECMO was higher, while mean duration of mechanical ventilation and ECMO and ICU length of stay were longer compared to the presented case [5]. However, due to the rarity and heterogeneity of postpartum complications requiring ECMO therapy, appropriate comparability is impossible.

Stabilization of vital functions is the priority in maternal critical illness. However, the vulnerable postpartum psychological condition should be treated with special attention by the ICU staff. An analysis of the US Amniotic Fluid Embolism Registry identified symptoms of post-traumatic stress disorder in 55.1% of amniotic fluid embolism survivors at 1-year follow-up [1]. The presented patient developed depressive symptoms during ICU stay which were treated with medications. She was primarily separated from her newborn child during critical illness; bonding was enabled lately during ICU stay. The risk for postpartum depression is increased after peripartum complications [4]. Few data exist on mothers' experiences in the ICU after complicated childbirth. In qualitative interviews, women reported devastation of being separated from their infant [6], which is associated with higher postpartum depression in neonatal ICU care [7]. A randomized controlled trial identified lower maternal postpartum depression by skin-to-skin contact after birth of premature infants [7]. Strategies to enhance contact after childbirth should be evaluated and integrated in adult critical care, if the condition of mother and infant allows it. Continuous information on the infant's situation are of high relevance for the mother [6]. Patient reported experiences should be considered to improve and individualize standards for family-centered care in postpartum critical illness. Adequate psychosocial support for the mother and her family is essential during this unexpected, life-threatening event.

This single patient case report is limited by the potential risk of overinterpretation and lack of generalizability.

Take-Home Messages

- Amniotic fluid embolism can present with disseminated intravascular coagulation, massive bleeding, and an inflammatory reaction and can lead to severe ARDS and multiorgan failure.
- Severe ARDS induced by amniotic fluid embolism in the postpartum period might require treatment with VV-ECMO and inhaled nitric oxide and result in a favorable outcome.
- The postpartum period is a vulnerable state for the mother regarding the risk for development of life-threatening somatic complications, as well as a psychological burden.
- Postpartum ICU treatment can lead to mother-newborn separation. Family-centered psychosocial support is essential during an unexpected event of critical illness after childbirth.

Summary

A 33-year-old female patient developed ARDS and multiorgan failure after complicated childbirth in an external hospital. According to the reports from the external obstetrics center, severe postpartum hemorrhage, symptoms of shock, and a sudden episode with a decrease in peripheral oxygen saturation to 80% were observed after regular delivery of the complete placenta. Compromised coagulation was described. After operative bleeding control, a sudden ventricular tachycardia with consecutive cardiac arrest and need for brief cardiopulmonary resuscitation was reported. Regarding the reported history of complicated childbirth and the symptoms, we considered amniotic fluid embolism as the most probable diagnosis for the complicated postpartum period with multiorgan failure including severe ARDS. Investigated differential diagnostics for ARDS included transfusion associated lung injury, aspiration, and infectious causes. Transfusion-associated lung injury diagnostic was negative. There were no findings suggestive for an aspiration of fluids into the central airways. In addition, the missing detection of pathogens in microbiologic specimens supported a non-infectious cause.

Multimodal management of severe ARDS with inhaled nitric oxide, prone positioning, and VV-ECMO resulted in a favorable outcome. Due to the rarity and heterogeneity of postpartum ARDS after suspected amniotic fluid embolism, appropriate comparability is challenging.

Stabilization of vital function is the priority in critical illness after childbirth, though also the psychologically vulnerable postpartum condition should be treated with special attention by the ICU staff. Having experienced this life-threatening event in the postpartum phase, the patient reported depressive symptoms. She was primarily separated from her newborn. Few data exist on mothers' experiences in the ICU after complicated childbirth with separation from their newborn. Patient reported experiences are essential to individualize standards for mother-newborn contact and family-centered care in postpartum critical illness.

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Management of a Non-traumatic Tracheal Lesion in Severe Tracheobronchomalacia

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Contents

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Learning Objectives

- The management of a non-traumatic tracheal lesion
- The management of complications during a conservative treatment strategy
- The value of VV-ECMO in non-ARDS patients

22.1 Introduction

Tracheal injury can occur after blunt and penetrating trauma, caustic inhalations, or healthcare procedures and is associated with high morbidity and mortality [1]. Among non-traumatic tracheal lesions healthcare procedures such as percutaneous dilatational tracheostomy, endotracheal intubation, or rigid bronchoscopy are most common. The early detection of a tracheal injury, an appropriate airway management, and the consideration of a surgical versus a conservative strategy are the key features of treatment.

In this case, we present a patient with severe tracheobronchomalacia due to polychondritis who experienced a large tracheal lesion during elective placement of an airway stent. In this context, we aim to highlight and discuss three relevant topics: (1) the management of a non-traumatic tracheal lesion, (2) the value of VV-ECMO in non-ARDS patients, and (3) the management of complications during a conservative treatment strategy.

Case Presentation

A 49-year-old male patient with severe tracheobronchomalacia due to polychondritis is presented. The onset of the polychondritis was 10 months before ICU admission with a rapid progress despite immediate initiation of a therapy with tocilizumab. During the further course, he developed a severe stenosis of the main and segmental bronchi on both sides so that he required repeated balloon dilatations. Due to the weak walls of the trachea and the right and left main bronchus, he experienced severe expiratory central airway collapse that caused dyspnea and led to retained secretions with recurrent pulmonary infections and a severely reduced FEV_1. During the further course, he received multiple placements of stents and the use of a home ventilator with continuous positive airway pressure (CPAP) was initiated. Due to the placement of self-absorbable stents, the procedure had to be repeated every 3–4 months.

He was now admitted for a planned re-placement of the stent. Under general anesthesia using total intravenous anesthesia, the glottis was visualized using a Kleinsasser laryngeal suction tube, and a jet ventilation was started. Several small defects in the stent could be seen, some with ingrowing granulation tissue with a stenosing effect. After pre-dilation with an airway dilation balloon (trachealator), a new bioresorbable stent was inserted. The remains of the old stent were then recovered with the forceps. However, an increasing mucosal lesion of the tracheal posterior wall, observed distal to the stent, progressively enlarged because of the applied jet ventilation

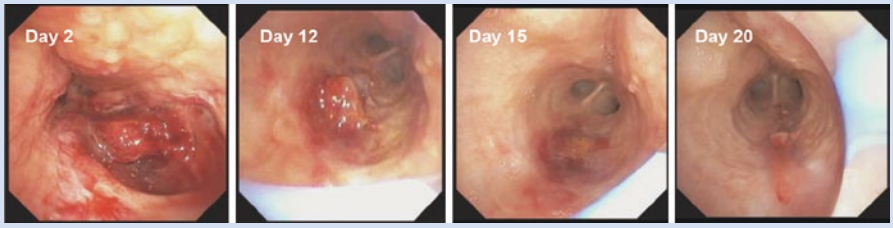

Fig. 22.1 Bronchoscopy finding at day 5, day 12, day 15, and day 20

(Fig. 22.1, left panel). An immediate interdisciplinary consultation with anesthesia, thoracic surgery, ear, nose and throat (ENT), and pneumology indicated that an over-stenting with a covered Y-stent would not be appropriate, and there were no options for a surgical therapy. Therefore, the team decided to intubate both main bronchi with small tubes (ID 4.0). However, due to deteriorating hypoxemia and hypercapnia, an emergency veno-venous ECMO was initiated by bifemoral cannulation (outflow cannula 25Fr/38 cm right, inflow cannula 19Fr/50 cm left). The initial ECMO blood flow was 4.5 L/min and sweep gas flow 2.5 L/min. Thereafter the patient was transferred to the intensive care unit.

22.2 Investigations

In this patient, the investigations focused predominantly on repeated bronchoscopies to continuously reassess the size and morphology of tracheal lesion (Fig. 22.1). In this regard, the tracheal lesion was evaluated as Level I injury according to the morphologic classification of Cardillo and colleagues [2] indicating a mucosal injury without mediastinal emphysema and esophageal injury. Further investigations included monitoring of inflammatory markers due to the high risk of mediastinitis, monitoring of the VV-ECMO to secure perioperative gas exchange and enable to minimize airway pressures, as well as repeated chest X-rays and CT scans (Fig. 22.2).

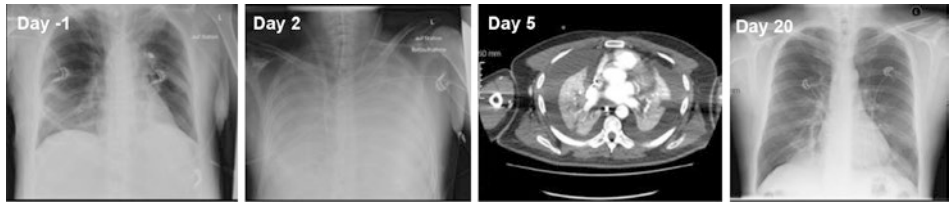

Fig. 22.2 Radiological findings before the intervention and during the ICU stay

22.3 Differential Diagnosis

Differential diagnoses for tracheal lesions are primary malignant or benign endobronchial lesions, endobronchial metastases, or non-neoplastic lesions such as amyloidoma or bronchial tuberculosis. In case of a suspected tracheal lesion, CT imaging and bronchoscopy are the most important diagnostic determinants. The CT can reveal a pneumomediastinum or subcutaneous emphysema while bronchoscopy, which is the "gold standard" diagnostic strategy, can provide the exact location and size of the tracheal lesion. As mentioned above, the lesion should be classified based on the depth of tracheal wall injury using a morphologic classification proposed by Cardillo and colleagues [2]. In case of a complete laceration of the tracheal wall, concomitant esophageal injury has to be excluded using upper gastroenterologic endoscopy and a CT scan of the chest with oral contrast.

22.4 Treatment

After ICU admission, a deep sedation was started aiming at a Richmond Agitation Sedation Scale (RASS) of −5 and a continuous administration of cisatracurium was provided to avoid spontaneous breathing and coughing. Due to a Level I injury, a conservative treatment strategy with continuously bronchoscopic evaluation, endotracheal tube cuff adjustment, and low airway pressures was chosen. The two tubes (one tube in each main bronchus) were removed under bronchoscopic supervision and replaced by a nasal intubation with a single tube (ID 7.5) that was placed with the tip 2 cm proximal to the tracheal lesion. Thereafter, the ventilator settings were changed aiming at near-apneic ventilation using airway pressure release ventilation (APRV) with P_{high} at 5 cmH_2O and P_{low} at 3 cmH_20, a respiratory rate of 8/min, and an inspiratory time of 3 s. An ECMO blood flow of 4 L/min was required to maintain a PaO_2 60 to 70 mmHg, while the sweep gas flow of 2.5 L/min was sufficient to maintain $PaCO_2$ in normal ranges. There were no signs for recirculation. However, there was frequently inadequate ECMO blood flow due to decreased venous return so that high volumes of fluids had to be administered. At ICU admission, the patient was in normal frequency sinus rhythm and required only low doses of vasopressors. A bedside transthoracic echocardiography showed normal LV and RV internal volumes and systolic function. Systolic pulmonary arterial pressure was in normal range, and there was no pericardial effusion. Routine 8-h measurements of blood and platelet counts, prothrombin time, and fibrinogen and antithrombin III levels were in normal range. Furthermore, basic liver and kidney function tests as well as plasma levels of

indicators for intravascular hemolysis such as cell-free hemoglobin, haptoglobin, and LDH were normal. Administration of heparin was started aiming at a therapeutic range of the PTT of 50–70 s. Enteral nutrition therapy via nasogastric tube was initiated on the first day after ICU admission. The patient had high urine output, so that high volumes of fluids had to be administered to replace these losses. Creatinine, urea, and electrolytes were in normal ranges. After material for microbial diagnostics was obtained, a calculated broad antimicrobial treatment with linezolid, meropenem, and caspofungin was applied due to the high risk of mediastinitis.

22.5 Evolution, Outcome, and Follow-Up

During the first days after ICU admission, the patient was highly dependent on ECMO, and ongoing frequent episodes with inadequate ECMO blood flow were challenging. Daily bronchoscopies showed that there was a very good healing tendency due to rapidly growing granulation tissue (Fig. 22.1), and radiology findings indicated no signs for mediastinal emphysema. However, the findings of chest X-ray indicated early a white lung as a consequence of the low airway pressures (Fig. 22.2, Day 2). A CT scan of the chest confirmed that both lungs were completely collapsed and there were large pleural effusions (Fig. 22.2, Day 5) being a further reason for increased fluid requirement during the first day of ICU stay. Consequently, the patient received chest drains on both sides. During the further ICU stay, inflammatory markers such as leukocytes, CRP, and PCT were still in normal ranges. After 2 weeks, the bronchoscopy findings showed that the tracheal lesion was closed so that lung recruitment was initiated (Fig. 22.1, Day 15). After interdisciplinary discussions, ventilator mode was changed to bilevel positive airway pressure and lung recruitment was conducted by stepwise and slowly increasing PEEP levels up to 13 cmH_2O while continuously screening for mediastinal emphysema. Driving pressure was also increased but kept below 10 cmH_2O. Lung recruitment was supported by repeated prone positioning for at least 16 h. During the further course, tidal volumes increased slowly up to 200 mL and chest X-ray as well as daily lung ultrasound indicated a good expansion of both lungs (Fig. 22.2, right panel). At this time, the sedation weaning was started reducing the doses by 10% each day aiming at a RASS of 0 to −1 and aiming at assisted spontaneous breathing. Consequently, ECMO dependency significantly decreased and ECMO blood and sweep gas flow could be reduced continuously. Mobilization of the patient was started using a seating and standing stabilizer. During the further weaning progress, the team discussed intensively about the options how to handle expiratory central airway collapse after reducing the PEEP and after potential extubation. Another placement of a new stent was considered inappropriate due to the large lumen of the trachea (Fig. 22.1, right panel). It was decided to gradually reduce the PEEP up to 5 cmH2O, to aim for a spontaneous breathing trial (SBT) and to apply nasal CPAP after extubation to keep the airways open. After approximately 3 weeks, the SBT was successful, and the patient was successfully extubated while still being on ECMO support. There were no signs for severe expiratory central airway collapse during CPAP (6 cm H_2O). Thereafter, ECMO sweep gas flow was turned off for 24 h and then ECMO was removed safely. Calculated antimicrobial treatment was stopped after 3 weeks. There

were no microbial findings so far. During the entire ICU stay, the patient did not develop any further organ failure. After 4 weeks, the patient was transferred back to the Department of Respiratory Medicine to continue tocilizumab treatment, adaptation of the home ventilator settings, and further rehabilitation.

22.6 Discussion

In this case, a 49-year-old male patient with tracheobronchomalacia due to polychondritis was presented who experienced a large non-traumatic lesion of the posterior tracheal wall during elective placement of an airway stent. As gas exchange could initially not be secured with a selective intubation of the left and right main bronchus, an emergency VV-ECMO was initiated by bifemoral cannulation. Due to a Level I lesion, a conservative treatment strategy was chosen instead of a surgical approach. The conservative approach focused on continuous bronchoscopic evaluation, endotracheal tube cuff adjustment, and low airway pressures [1]. Although outcome data of conservative and surgical approaches are still limited, there is increasing evidence that conservative approaches might not be inferior. Only patients with esophageal wall prolapse or patients who have worsening subcutaneous emphysema, pneumomediastinum, or pneumothorax should be considered for surgical treatment. The key determinant of the conservative approach is to minimize airway pressures and positive end-expiratory pressure [3]. In this regard, in our case the use of VV-ECMO secured gas exchange and allowed to apply a very low PEEP and driving pressures. In this respect, we observed a rapid closure of the lesion within 2 weeks after the tracheal injury. While there is increasing evidence of a benefit of VV-ECMO in patients with ARDS, the value of VV-ECMO in non-ARDS patients is unknown. However, our case suggests that the use of VV-ECMO in patients with a tracheal lesion might be beneficial but selection criteria for patients need to be defined in the future. As in our case, a conservative approach with very low airway pressure might be accompanied with further challenges such as collapsing lungs with large pleural effusions. After inserting chest drains, we decided to slowly increase PEEP and while keeping driving pressure below 10 cmH2O. As prone position during ECMO is supposed to be safe and is associated with improved outcome, prone positioning was initiated to enhance lung recruitment [4]. In this regard, within 7 days after starting lung recruitment, gas exchange was good and chest X-ray and lung ultrasound indicated fully expanded lungs. Interestingly, the patient could be extubated after approximately 3 weeks despite this complex treatment with temporary deep sedation and avoidance of early spontaneous breathing. This might be due to the intensive mobilization efforts after the decrease of ECMO dependency and due the absence of sepsis, underlining the important role of inflammatory process in terms of critical illness myopathy.

In summary, our case suggests that the use of VV-ECMO in patients with a tracheal lesion was safe and allowed to tolerate very low airway pressures which might have enhanced the healing process and therefore might be considered in these patients to support a conservative treatment strategy.

Take-Home Messages

- Tracheal lesions, even large ones, can be managed without operation, but such treatment need a highly skilled multi-disciplinary and multi-professional team.
- In large tracheal lesion, ECMO therapy may be necessary to ensure low airway pressure, so it should be established early.
- Even in total collapsed lungs, prone positioning may be helpful to recruit parts of the lungs. Thus, it can be a treatment option.
- Absence of inflammatory process, like sepsis, and early mobilization may be beneficial to avoid critical illness myopathy.

Summary

A 49-year-old male patient with severe tracheobronchomalacia due to polychondritis experienced a large lesion of the posterior tracheal wall during elective placement of an airway stent. After emergency intubation of both main bronchi, the patient immediately received veno-venous extracorporeal membrane oxygenation (VV-ECMO) using femoro-femoral cannulation. After transferring him to the intensive care unit, a conservative treatment strategy with continuously bronchoscopic evaluation, endotracheal tube cuff adjustment, and very low airway pressures was chosen. There were no infectious complications but both lungs did completely collapse along with large pleural effusions as a result of the resting lungs. Repeat bronchoscopies showed that there was a good healing tendency, and follow-up radiology findings indicated no signs for mediastinal emphysema. During the further course, the patient received chest drains, the PEEP and driving pressure were stepwise and slowly increased again, and repeated prone positioning was started to support lung recruitment. Thereafter, the sedation was slowly reduced and assisted spontaneous breathing was promoted. After approximately 3 weeks the patient was successfully extubated while still being on ECMO support. Thereafter, ECMO sweep gas flow was turned off for 2 days and then the VV-ECMO could be safely removed.

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Post COVID-19 Bronchopleural Fistula Treated with "Closed-Lung" Minimal Ventilation and $ECCO_2R$: A Clinical Case Report

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Contents

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Learning Objectives

- What is a closed-lung strategy
- How $ECCO_2R$ can be clinically implemented
- Risks and benefits of $ECCO_2R$
- How to assess a chest tube functionality

23

23.1 Introduction

Bronchopleural fistula is a relatively common, yet complex, disease. This condition often represents a challenge for physicians since diagnosis can be tricky. Moreover, there is a lack of consensus on the optimal management and treatment [1].

This condition can occur acutely, sub-acutely, or in the advanced phase of lung disease. While the subacute and chronic forms more often develop after infectious processes in comorbid or immunocompromised patients and its clinical course is milder with fever, malaise, and wasting, the acute form can be a life-threatening condition leading to tension pneumothorax or acute refractory hypoxemia.

Acute forms most commonly develop after pulmonary surgery or interventions, and the fistula is usually located on the surgical suture. Right pneumonectomy shows a greater risk of postoperative bronchopleural fistula due to the more extensive resection required [2].

The most common clinical features of the acute form include sudden onset of dyspnea, hypotension, expectoration of purulent fluid, persistent air leak, and the reduction or disappearance of pleural effusion on chest radiograph.

Bronchoscopy usually allows confirmation of air leak and can be used to evaluate the surgical site and localize the fistula. CT scan is another important, albeit not always feasible, diagnostic tool in critically ill patients.

Management strategy is aimed to address any immediate, life-threatening manifestation of such condition. Surgery often represents an effective solution with excellent success rate since most of bronchopleural fistulas occur early after surgery and are not infected yet. Surgical techniques include vascularized muscle flap coverage for direct closure and decortication, thoracoplasty, or even conversion to pneumonectomy to decrease the air leak [3]. Bronchoscopic approaches are also an available solution, though their success rate is variable, making it an appropriate alternative for those patients not suitable for surgery or as a bridging therapy to curative surgery [4, 5].

Finally, intensivists should be aware that bronchopleural fistula clinical course is more complex in patients on positive pressure mechanical ventilation. Airway pressures shall not exceed the critical opening pressure of the fistula to allow its healing. When alveolar ventilation and gas exchanges become insufficient, other available solutions comprise double-lumen tubes or bronchial blockers for selective lung ventilation, high-frequency jet ventilation with permissive hypercapnia, $ECCO_2R$, or ECMO to allow lung rest.

Case Presentation

Our patient was a 59-year-old man who presented to the ER of a peripheral hospital for respiratory symptoms and fever. He tested positive to SARS-CoV-2 and was admitted to the infectious disease ward for bilateral interstitial pneumonia. Helmet CPAP therapy was early initiated and maintained for 7 days, though clinical response was poor. A CT scan showed pneumomediastinum and he was transferred to the ICU for further treatment, although intubation was delayed mainly due to patient refusal. He was finally intubated after few days and put on mechanical ventilation and a chest tube was positioned.

CT scan monitoring of pneumomediastinum showed no improvement, and the patient was transferred to our ICU in accordance with our hospital's thoracic surgery service.

After admission, an attempt of extubation was made but eventually failed and he was reintubated soon afterward due to respiratory failure and inability to maintain spontaneous breathing.

Few days later, our patient developed sudden desaturation, a sharp tidal volume reduction and respiratory acidosis with unmeasurable $PaCO_2$. Together with the thoracic surgeon, an additive, urgent anterior chest tube was positioned, though with limited clinical effect. Further evaluation and treatment were then necessary.

23.2 Investigations

The most clinically meaningful, bedside evaluation was the examination of the chest tube drainage system. The patient had a triple chamber drainage system (Fig. 23.1), which consists in a chamber dedicated to the water seal system (*Bulau's valve*), a second chamber dedicated to the collection of the effusion and a third chamber where the aspiration pressure level can be set with a water column.

When draining an air collection from the pleural cavity, intermittent bubbling should be detected in the sampling chamber in synchrony with the respiratory phase when transpleural pressure becomes positive (i.e., during expiration when on spontaneous breathing, during inspiration when on positive pressure mechanical ventilation). If no bubbles are detected, it can either mean that the whole air collection was drained or that the chest tube is mispositioned or occluded. Differential diagnosis can be made by observing the water seal column: if an oscillation of the latter can be seen in synchrony with transpleural positive pressure phase, it means that the chest tube is still well positioned, and the air collection was completely drained.

When continuous bubbling in the sampling chamber is detected, this means there is a continuous air leak, which is most commonly due to bronchopleural fistula. If on mechanical ventilation, monitoring air leak percentage and value from the ventilator is the following step.

At this point, the diagnosis of bronchopleural fistula on our patient was suspected and he underwent a CT scan which confirmed our hypothesis (Fig. 23.2).

Fig. 23.1 Triple chamber chest drainage system available at our center. Black arrow indicates water seal chamber. In this chamber intermittent bubbling shall be detected or, at least, oscillation of water column in synchrony with respiratory rate. Green arrow indicates collection chamber for effusions. Red chamber indicates the aspiration chamber where a water column is seen in order to regulate negative pressure values

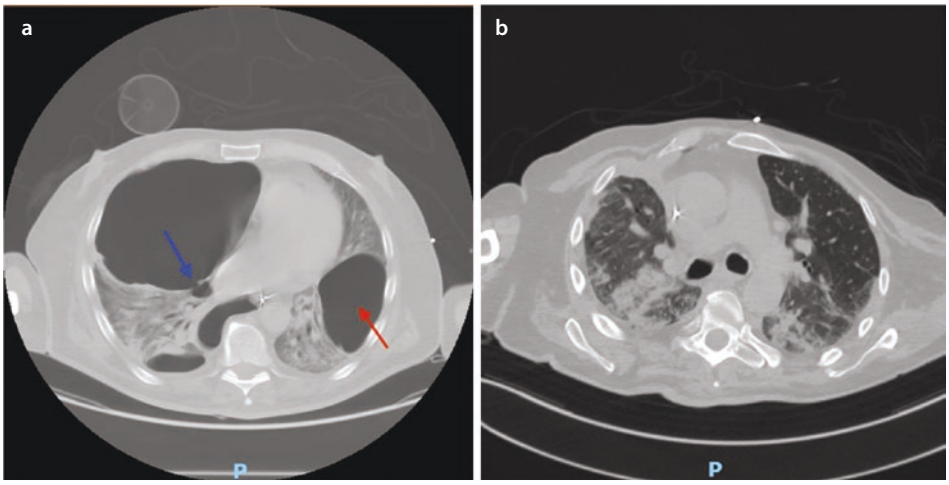

Fig. 23.2 **a** and **b** On the left, CT scan confirms bronchopleural fistula. Blue arrow indicates a massive pneumomediastinum collection and probably the bronchopleural fistula. Note that the exact leak could not be indicated with certainty due to the small dimension of the latter. Red arrow indicates a large pneumatocele in the contralateral lung. On the right, last CT scan before discharge showing lung adherent to pleural cavity wall

23.3 Differential Diagnosis

Relevant differential diagnoses to think of in such a clinical presentation were as follows:

- Massive pulmonary embolism: clinical presentation can be very similar to that of an acute bronchopleural fistula, especially for what concern hemodynamics and chest mechanics. Moreover, our patient already suffered from segmentary pulmonary embolism on entrance at the peripheral hospital. His clinical condition included many risk factors for further worsening of his coagulation asset, such as prolonged bed rest and immobilization, inflammatory state, and SARS-CoV-2 infection.
- Acute occlusion or dislocation of the chest tube: chest tube occlusions occur rather often due to clot formation or even fibrinoid material accumulation. Mispositioning can occur due to patients' movements or changes in the chest anatomy after draining conspicuous collections. In addition to that, mobilization of critical ill patients in intensive care is often challenging, especially when clinically unstable. During these maneuvers, mispositioning can occur.

23.4 Treatment

There is still a lack of consensus on the optimal treatment for acute bronchopleural fistulas. Positioning of a chest tube, if not already present, and avoidance of life-threatening conditions such as tension pneumothorax and pulmonary flooding are gold standard. Still, curative treatment remains non-univocal and must be tailored on a single case basis.

Although surgery represents a solid solution with excellent success rate in patients with surgical anastomosis dehiscence, our patient clinical condition was extremely poor, and perioperative risk was considered too high. Moreover, the fistula was estimated around 8 mm and was possibly suffering from bacterial infection and the evaluation of risks and benefits brought to a conservative strategy.In this sense, we decided to apply a "closed-lung" minimal ventilation, namely, a strategy aimed at reducing airway pressures below the critical opening pressure of the fistula, and allow the healing of the latter [6]. However, this strategy notably reduces alveolar ventilation. Our patient had already suffered from bilateral pneumonia and fibrotic organization was already progressing. This concurred to a $PaCO_2$ elevation above permissive hypercapnia levels (pH < 7.20) and an extracorporeal decapneization treatment was necessary.

23.4.1 "Closed-Lung" Minimal Ventilation Strategy

We deepened sedation and treated our patient with paralyzing agents such as rocuronium in drip infusion.

Previous ventilation mode and ventilatory parameters were pressure control ventilation with Pcontrol 26 cmH_2O, PEEP 5 cmH_2O, RR 23, and Vte 220 mL. Stable peak pressure and driving pressure were hard to determine because of the air leak, but estimated mechanical power was 16 J/min. P/F ratio before initiating "closed-lung" minimal ventilation was 181 (FiO2 1). We therefore reduced Pcontr to 16 cmH_2O and tidal volume reached 3 mL/Kg of PBW (circa 250 mL); PEEP was adjusted to 3 cmH_2O, RR 16, and I:E ratio of 1:1.2. FiO2 was set at 0.8 and progressively reduced throughout the treatment.

With these values, we produced a driving pressure of 9 cmH2O and a peak pressure of 20 cmH2O. Recalculated mechanical power was 6.1 J/min.

More importantly, we could verify that airway pressures were kept below the critical opening pressure of the fistula by examining the chest tube draining system: indeed, with such mechanical power, continuous bubbling was not detected, while intermittent oscillation of water seal column was evident. Chest tube drainage system was kept open and on simple underwater seal in the beginning of our treatment. No major air leaks were detected by the ventilator. At this point, with these three elements we could tell with a fair degree of certainty that the fistula was not open anymore and the spontaneous healing process could initiate. After few days the drainage system was put on active suction to ensure the drainage of any further air leak from chest cavity.

23.4.2 Low-Flow $ECCO_2R$

Extracorporeal CO_2 removal made our ventilation strategy possible. In such patients, $PaCO_2$ can build up very quickly, and uncompensated respiratory acidosis might play a key role in an already critical balance between minute ventilation and cardiac output.

Obviously, such an invasive treatment brings in risks which must always be weighted. In particular, such blood flow values require the positioning of a high flow

dialysis catheter and continuous systemic heparin therapy, which exposes patients to the risk of major bleeding. Coagulation asset must be tested every 6 h and heparin infusion was modulated accordingly to our hospital protocol.

We put our patient on CRRT machine with in-parallel low-flow CO_2 filter. Blood flow (Qb) was set at 400 mL/h and gas flow of pure oxygen on the filter was set at 6 L/min as per technical sheet of the product.

23.5 Evolution, Outcome, and Follow-Up

Decapneization therapy was carried on for 10 days in total. Our patient also underwent a cycle of pronation.

He was progressively weaned from decapneization treatment by reducing blood and gas flow accordingly to pH levels, $PaCO_2$ levels, and ventilation values. We alongside progressively augmented alveolar ventilation (up to 6 mL/Kg of PBW) without exceeding in airway pressures and constantly monitoring our drainage system chambers. Our aim was to simultaneously decrease extracorporeal CO_2 removal and increase alveolar ventilation in order to maintain constant matching between minute ventilation and cardiac output. Sedation was enlightened, rocuronium infusion was stopped, and the patient was put on pressure support. He was finally disconnected from $ECCO_2R$ with good clinical response.

Percutaneous tracheostomy was made on the 21st day. Such delay was due to an excessive bleeding risk during heparin infusion for $ECCO_2R$. A physical and respiratory therapy program was undertaken with good results. Family visits were also allowed with notable positive emotional impact on our patient.

Our patient was finally discharged on the 51st day with low oxygen therapy on tracheostomy tube and good functional and radiological status (◘ Fig. 23.2).

23.6 Discussion

This case includes features of clinical relevance for young intensivists, especially for those working in respiratory and COVID ICUs.

Probably the most important feature of acute bronchopleural fistula is clinical presentation, differentials, and prompt diagnosis. When diagnosed, treatment of emergent, life-threatening condition must be rapidly undertaken. As soon as stabilized, a curative treatment must be individuated.

In this case, we had multiple factors to keep into account. Our patient's clinical condition was indeed very unstable and probably too fragile to face surgery. Moreover, his pulmonary parenchyma had already been heavily challenged and altered by his previous pneumonia. The presence of several subpleural bullae and a worrying contralateral pneumatocele, in addition to previous prolonged high positive pressure ventilation strategies (CPAP, NIV, and double lung invasive mechanical ventilation), brought us to choose a conservative strategy, which turned out successful in the end.

Overall clinical management of such patients is complicated and requires constant care and attention. However, closed-lung ventilation in association with low-flow $ECCO_2R$ actually gave a chance to our patient to heal with spontaneous first

intention closure of the fistula while on positive pressure mechanical ventilation, without major impact on his acid-base equilibrium. Many risk factors accompany this treatment, but the overall risks/benefits evaluation correctly lead us toward an admissible goal.

In conclusion, this case report aims to present a feasible, yet delicate and challenging alternative, curative treatment for bronchopleural fistula in those patients who may not be eligible neither for surgery nor for endobronchial treatment.

Take-Home Messages

- Bronchopleural fistula can be difficult to diagnose but must be promptly recognized due to the high risk of potentially catastrophic evolution
- Young intensivists shall be confident with chest tube drainage system evaluation in order to quickly and clinically recognize bronchopleural fistula.
- While first-line therapy should address life-threatening conditions such as tension pneumothorax and pulmonary flooding, a curative treatment must be undertaken in order to allow the closure of the fistula.
- A feasible, non-surgical nor interventional curative treatment for fragile patient is a closed-lung ventilation strategy in association with extracorporeal CO2 removal.

Summary

This case report aims to present a feasible, yet delicate, and challenging alternative for curative treatment of bronchopleural fistula in those patients who may not be eligible neither for surgery nor for endobronchial treatment.

Bronchopleural fistula is a relatively common condition which young intensivists may encounter, especially in respiratory and COVID ICUs. This condition most commonly occur acutely, leading to life-threatening conditions such as tension pneumothorax and pulmonary flooding. While first-line interventions aim to treat such conditions, a curative therapy must be undertaken. Surgery represents a valid solution, while bronchoscopic tools such as endobronchial blockers present more variable success rate and are usually indicated for small fistulas.

Our patient was a 59-year-old man who was previously admitted to a peripheral hospital for SARS-CoV-2 pneumonia. He soon developed pneumomediastinum and was transferred to our ICU for further treatment. He was sedated and intubated for respiratory failure but rapidly developed a bronchopleural fistula.

Since his clinical and previous pulmonary condition was considered too poor both for surgery and bronchoscopic procedure, we adopted a closed-lung ventilation strategy in association with $ECCO_2R$ treatment in order to reduce mechanical power and allow first intention closure of the fistula while maintaining clinically acceptable values of PaCO2 and pH.

Our patients successfully recovered and was discharged after 51 days on low-flow O2 therapy.

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Weaning from Mechanical Ventilation: Antipsychotic-Induced Respiratory Dyskinesia in a Patient with Severe SARS-CoV-2 Pneumonia

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Contents

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Learning Objectives

- Tachypnea is a common clinical sign of patient distress. It is associated to acute illness, such as respiratory failure, heart or CNS dysfunction, delirium, or infection.
- In mechanically ventilated patients, the presence of tachypnea suggests the onset of an unexpected clinical problem that should be addressed before attempting to wean ventilatory support.
- Tachypnea may have no evident cause in some patients. Tachypnea of unknown cause requires a wide diagnostic march to identify the underlying cause.
- Tardive dyskinesia (TD) is an uncommon side effect of chronic antipsychotic therapy. Although the classical manifestation involves oromandibular or limb muscle. Isolated involvement of respiratory muscles had been described and poses a clinical challenge.

24.1 Introduction

In the ICU setting, weaning from respiratory support is a common challenge among patients who undergo long-term invasive mechanical ventilation. Persistence of lung disease, upper airway pathology, heart failure, delirium, and acquired myopathy are common complications during weaning of ventilatory support [1]. Persistent tachypnea and abnormal breathing patterns occasionally complicate extubation and require an extensive differential diagnosis to identify the underlying cause.

Among the possible complications of long-term antipsychotic medication, respiratory dyskinesia is an underdiagnosed and poorly understood manifestation of TD affecting the diaphragm and accessory respiratory muscles, which manifests as a paradoxical and inefficient respiratory pattern, leading to respiratory failure [2].

The authors report a case of a patient with severe SARS-CoV-2 pneumonia who developed clinical features compatible with isolated respiratory dyskinesia complicating weaning from ventilatory support.

Case Presentation

A 62-year-old female patient with confirmed SARS-CoV-2 infection was admitted to the emergency department with increasing shortness of breath, dry cough, fever, myalgia, and dysgeusia over the past 9 days. Her past medical history included a diagnosis of paranoid schizophrenia over 30 years ago, initially treated with haloperidol which was discontinued due to unspecified side effects. In the past 2 years her psychiatric illness was controlled with paliperidone palmitate (50 mg IM monthly) plus oral risperidone (2 mg od), under which the patient was clinically stable and was able to maintain a job and perform her daily activities. No illegal drug use or other previous illnesses were reported, and the patient did not take any other medication.

An initial evaluation in emergency department identified severe acute respiratory failure with severe hypoxemia (SpO2 89–90% under non-rebreather mask 15 L/min) and shallow breathing

pattern with over 40 bpm. A chest radiography showed bilateral lung infiltrates compatible with SARS-CoV-2 pneumonia. A trial of noninvasive ventilation failed due to ineffective breathing and worsening hypoxemia. The patient was sedated, intubated, and transferred to our ICU, where she received optimized care (lung-protective ventilation, neuromuscular blocking agents and 16-h long periods of prone-positioning for 5 days, a 10-day course of dexamethasone and remdesivir, adequate sedation, nutrition, and organ support as needed). The patient developed ventilator-associated tracheobronchitis by methicillin-sensible *Staphylococcus aureus* as a complication of mechanical ventilation, which was treated with flucloxacillin.

On the seventh day of ICU care, the patient consistently presented signs of improved oxygenation and began weaning of sedation and ventilator support. The weaning progression, however, was limited due to severe tachypnea (50-60 bpm) with paradoxical respiration and subsequent worsening of oxygenation. Risperidone treatment had been maintained since ICU admission. The hypothesis of delirium was considered and quetiapine was introduced in increasing doses (up to 100 mg tid), as well as oxazepam (up to 50 mg tid), with no improvement over the following days. A trial of dexmedetomidine titrated to 1.22 mcg/kg/h was also attempted with no success.

Aside from the abnormal respiratory pattern, the patient exhibited subtle peribuccal and glossal fasciculations. The remaining physical examination was unremarkable.

Having no identifiable cause for this respiratory pattern and frequency, a thorough diagnostic process was initiated to exclude potential secondary causes. Serial arterial blood gases did not show any major acid-base disturbances. Serial chest radiographies documented a favorable evolution of SARS-CoV-2 pneumonia. A chest CT scan revealed scarce ground glass opacities compatible with the expected resolution of viral pneumonia; IV contrast found no pulmonary embolism. A head CT did not show any remarkable findings. An echocardiogram was performed, identifying eccentric left ventricular hypertrophy with minor intraventricular gradient but no other findings suggestive of heart failure or pulmonary hypertension. A trial of spontaneous breathing and extubation was also attempted, which resulted in early extubation failure due to persistent paradoxical respiration with worsening hypoxic respiratory failure. Video laryngoscopy was performed at the time of reintubation, revealing normal airway anatomy without any significant findings. Ultrasound evaluation of the diaphragm was attempted during assisted pressure mechanical ventilation; however, the high respiratory effort impacted image acquisition and the resulting images were considered to have insufficient quality for an adequate interpretation.

Plausible causes of hyperventilation and abnormal respiratory pattern weren't clearly evident. Our team had already addressed delirium, anxiety, and withdrawal syndromes through the introduction of antipsychotics, benzodiazepines, and dexmedetomidine with no effect. During periods of light sedation, the patient was conscious and aware of her surroundings and could obey simple commands, but was unable to control her own respiratory effort. CAM-ICU was consistently negative. When asked, the patient referred respiratory distress. Adequate oxygenation and ventilation

were guaranteed under assisted-mode mechanical ventilation with low PEEP and FiO2. Other ventilator strategies were tried with no benefit, as the patient's own respiratory drive consistently triggered an assisted breath.

A chest CT scan and echocardiogram were performed to formally exclude any intrinsic factors contributing to a notion of dyspnea or tachypnea through a hypoxic or mechanoreceptor-mediated stimulus. The respiratory pattern persisted despite the presence or absence of orotracheal intubation, and the presence of tachypnea and abnormal respiratory pattern without upper airway pathology hinted at an underlying neurological etiology. A normal head CT excluded acute events that could lead to a CNS-mediated hyperventilation response; thus a pharmacological cause seemed plausible. A diagnosis of respiratory dyskinesia secondary to chronic risperidone and paliperidone therapy was proposed considering the long-term use of antipsychotics with high dopamine-2 (D2) receptor antagonistic effect and previous history of uncharacterized side effects secondary to haloperidol. This hypothesis was presented to a multidisciplinary team and a therapeutic trial was conducted according to the best known practices.

Given the possible diagnosis of respiratory dyskinesia, all previously prescribed antipsychotic drugs (risperidone, quetiapine) and oxazepam were withdrawn. Paliperidone, which had been administered 12 days before hospital admission, was also discontinued. A prescription of tetrabenazine (titrated to 25 mg tid) and clonazepam (titrated to 2 mg tid) was initiated. Due to concerns of relapsing psychotic symptoms, clozapine (an antipsychotic drug with a low antagonistic D2 receptor effect) was also initiated and titrated to 75 mg daily.

After initiation of the mentioned pharmacologic regimen on the 19th day of ICU care, the patient improved her respiratory pattern over the course of the following days. Motor and respiratory physiotherapy were intensified as soon as the patient showed signs of clinical improvement. A tracheostomy was performed on the 24th day of ICU care due to prolonged intubation time and to facilitate weaning from ventilator support. Complete withdrawal from respiratory support was possible on the 32nd day of ICU care. All signs of respiratory dyskinesia and oral fasciculations were absent at this point. The patient was discharged from the ICU ward after 35 days of care.

During the remaining hospitalization, the patient continued motor and respiratory rehabilitation therapy with marked improvement of muscular function. Weaning from tetrabenazine and clonazepam was possible and both drugs were discontinued without any tardive symptoms. The patient was discharged home after 48 days of hospitalization with no relevant sequelae, medicated with clozapine 75 mg once daily. One month after discharge, the patient had completely recovered to her previous status and maintained a stable psychopathological status.

24.2 Discussion

This case demonstrates a situation of respiratory dyskinesia, an uncommon and potentially lethal manifestation of TD. TD is a broad spectrum of motor disorders associated with prolonged use of dopamine-blocking agents which are characterized by involuntary and irregular movements with varying degrees of intensity, from twitching or writhing movements to choreiform jerks. It has been theorized that the chronic blockade of D2 receptors in motor striatum may promote aberrant synaptic plasticity through the production of excessive and hypersensible D2 receptors which lead to an intense stimulation when dopamine is released, promoting hyperkinetic movements [2, 3].

Although tardive symptoms may present as early as 1 month after initiation of continuous antipsychotic therapy, TD typically presents between the first and second year of continued medication, and the classical manifestation involves the facial and oromandibular muscles (80%). Involvement of trunk, diaphragm, and accessory respiratory muscles has a 3.9% of prevalence among patients undergoing antipsychotic medication and may rarely occur in the absence of the classical features of TD [4–6]. Respiratory dyskinesia is characterized by a fast, irregular, and uncoordinated respiratory pattern. The inefficient breathing pattern leads to low tidal volumes and excessive dead space ventilation, worsens gas exchanges, and, ultimately, evolves to respiratory failure [5].

There are no established guidelines that address the treatment of TD. All authors recommend the withdrawal of all previously prescribed antipsychotics and drugs with potential dopamine receptor blocking effects or anticholinergic effects due to the possibility of causing or exacerbating dyskinesia. If there is a risk of worsening psychotic illness, alternative antipsychotic therapies are limited to second-generation antipsychotic drugs with lowest antagonistic D2 receptor effect, such as clozapine and quetiapine [3, 6]. If dyskinesia persists, other therapeutic options may be explored. Tetrabenazine, a monoamine-depleting agent, has been used in similar case reports with success. Long-acting benzodiazepines are used as an adjunct, due to their muscle-relaxant and anxiolytic/sedative proprieties. [3] Deep brain stimulation may be considered for severe cases [6].

Our patient developed TD related to risperidone and paliperidone with unequivocal tardive symptoms during the ventilation weaning in the ICU. However, since the patient's respiratory symptoms coincided with symptomatic SARS-CoV-2 infection, we were unable to clearly determine the onset of tardive symptoms. We found no association between COVID infection and respiratory dyskinesia or other tardive symptoms in the literature.

To our knowledge, only a single case with comparable clinical features was reported in an ICU setting in the advent of a desipramine overdose [7]. While tardive syndromes occasionally occur in a psychiatric setting, it is important to consider that intensive care physicians are unfamiliarized with the side effects of long-term antipsychotic use and rarely encounter patients with complex iatrogenic complications of antipsychotic drugs. A high index of suspicion is necessary to accurately determine the diagnosis and establish effective treatment.

Take-Home Messages

- Weaning of ventilatory support is challenging. Patients may be difficult to wean due to several causes, the most frequent being delirium, lung disease, and undiagnosed heart failure.
- The most common neuromuscular entity complicating ventilatory weaning is ICU-acquired neuropathy/myopathy. Other causes are far less common.
- Differential diagnosis of difficult to wean patients is wide and may require extensive diagnostic work-up to identify the underlying cause.
- Respiratory dyskinesia is a form of TD that involves all respiratory muscles. It manifests as a paradoxical, shallow breathing pattern, leading to respiratory failure.
- Respiratory dyskinesia is an underdiagnosed and poorly understood complication of chronic antipsychotic medication which may present at any stage of treatment.
- Tardive symptoms may present as early as 1 month after initiating continuous antipsychotic treatment.
- Early diagnosis of respiratory dyskinesia and suspension of drugs with potential dopamine receptor blocking effects or anticholinergic effects are necessary to improve symptoms and avert long-term complications.
- TD which persists despite drug suspension may respond to a therapeutic trial of tetrabenazine. Long-acting benzodiazepines or deep brain stimulation are valid treatment options in difficult to treat patients.
- If there is a risk of worsening psychotic illness, alternative antipsychotic therapies are limited to second-generation antipsychotic drugs with lowest antagonistic D2 receptor effect.
- Complications of long-term psychiatric therapy are rare in the ICU setting. A multidisciplinary approach to challenging clinical cases provides an invaluable value to differential diagnosis, therapeutic options, and patient outcome.

Summary

A 62-year-old woman with a previous history of paranoid schizophrenia controlled with antipsychotics was admitted under ICU care due to acute respiratory failure secondary to SARS-CoV-2 pneumonia. During ventilatory weaning, the patient presented tachypnea with paradoxical breathing. After excluding delirium, upper airway, lung, and CNS complications, the diagnosis of respiratory dyskinesia was considered. Cessation of chronic antipsychotic medication and introduction of tetrabenazine and clonazepam markedly improved the patient's respiratory pattern, allowing weaning of ventilatory support and a good recovery. From a psychiatric point of view, clinical stability was possible with the introduction of clozapine.

Respiratory dyskinesia is a potentially lethal manifestation of TD, with a 3.9% prevalence among patients undergoing antipsychotic therapy. Patients develop a fast and uncoordinated respiratory pattern causing shallow breathing and respiratory failure. While there is no well-defined treatment strategy for tardive symptoms, published reports support the cessation of drugs with potential dopamine receptor blocking effects and the role of tetrabenazine in the management of this syndrome.

Complications of long-term psychiatric therapy are rarely seen in an ICU setting. A high suspicion index and an early multidisciplinary approach is helpful to establish a definitive diagnosis and ensure the best outcome.

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Pulmonary Embolism in the ICU

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Contents

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Learning Objectives

- Definition and epidemiology of pulmonary embolism
- Pathophysiology of pulmonary embolism, right ventricular failure, and their determinants on patients' outcome
- Right ventricle—protective management of acute pulmonary embolism in intensive care
- Multidisciplinary diagnostics of pulmonary embolism
- Treatment of pulmonary embolism in the ICU setting
- How to set a right ventricle targeted protective mechanical ventilation

25.1 Definition, Causes, and Epidemiology of Pulmonary Embolism

Pulmonary embolism (PE) refers to the obstruction of the pulmonary artery or one of its branches by pathologic material (e.g., thrombus, tumor, air, fat) that originates elsewhere in the body and migrates through the systemic circulation and the right heart to the lungs.

Acute PE has a reported annual worldwide incidence of 0.7–2.7 per thousand adult humans per year, a high recurrence rate, and a negative impact on survival. Behind myocardial infarction and stroke, PE is the third most frequent acute cardiovascular syndrome [1]. Nowadays, following more effective therapies and interventions and better adherence to guidelines [2, 3], case fatality rates for acute PE may be decreasing. However, considering the high sensibility of new diagnostics tools, there is also a tendency toward overdiagnosis of not clinically significant events.

Pulmonary embolus can directly originate from the right atrium and cause cardioembolism, often subsequent to atrial fibrillation, but also related to other predisposing causes as atrial aneurysm, right ventricle dysplasia, rheumatic valve disease, dilated cardiomyopathy, and akinetic/hypokinetic myocardial segments. However, acute PE originates most commonly in the deep veins of calf and thigh, though in less than 10% of cases the embolic thrombus originates in the upper extremities. This kind of PE originated from the vein is also named venous thromboembolism (VTE). An extensive list of environmental and genetic predisposing causes can lead to VTE.

- Major risk factors (odds ratio, OR > 10) include recent hospitalization, trauma, surgery, cancer, myocardial infarction, heart failure, atrial fibrillation, and immobilization that overall contribute for approximately 70% of the disease burden.
- Moderate risk factors (OR 2–9) cover specific genetic mutations including severe inherited thrombophilia (e.g., factor V Leiden, prothrombin gene mutation 20210, antithrombin deficiency, protein C or protein S deficiency, and the antiphospholipid antibody syndrome). These factors account for approximately 7% of VTE. Other pathological conditions (e.g., autoimmune diseases, infections, inflammatory bowel diseases, stroke) and pregnancy as well as medications (e.g., chemotherapy, hormone replacement therapy) are also listed among the moderate risk factors; however, they contribute for a lower percent of the disease burden.
- Weak risk factors (OR < 2) consist of age as well as more common cardiovascular risk factors such as obesity, hypercholesterolemia, hypertension, and diabetes

mellitus. The risk of VTE rises with the increase in age, where the incidence of VTE is almost eight times higher in individuals older than 80 years than in the general population. VTE may be viewed as a possible component of the cardiovascular disease (CVD). Risk factors that are common to CVD are weak risk factors for VTE.

As clinical judgment lacks standardization, several explicit clinical prediction rules have been developed. Among others, the *Wells' criteria* [4] and the *revised Geneva clinical prediction* [5] are both based on patient's risk factors and clinical findings such as age, previous DVT or PE, surgery, malignancy, immobilization, heart rate, PaCO2, PO2, and chest X-ray.

Uncommon causes of VTE can be difficult to diagnose and can need specific treatment that differs from standard management. An interesting clinical case of uncommon PE is reported and discussed in ▶ Chap. 27, where PE is caused by the pulmonary embolization of a hydatid cysts atypically located in the right atrium. In this context, imaging is critical for the right diagnosis process. The remaining 20% of PE events occur in the absence of identifiable risk factors. Patients with unprovoked PE are usually younger than other PE patients.

The last European Guidelines for diagnosis and management of PE have been provided by the European Society of Cardiology in collaboration with the European Respiratory Society in 2019 [7].

25.2 Pathophysiology and Determinants of Outcome

Acute PE affects both hemodynamics and pulmonary ventilation/perfusion match with sudden increase in dead space and negative impact on gas exchange. The right ventricle suddenly faces a surge in afterload due to a critical increase in pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). It is important to highlight that the increase in PAP and PVR derives not only from a massive anatomical obstruction of the pulmonary circulation, but also from other coexisting factors: (1) the diffuse and strong pulmonary vasoconstriction induced by a significant release of thromboxane A2 and serotonin at a local level in the pulmonary vasculature and (2) the hypoxic pulmonary vasoconstriction in the affected lung areas. These two concomitant factors contribute to a further increase in PVR. The sudden and severe increase in PVR results in RV dilation and failure and leads to leftward bowing of the interventricular septum, negatively affecting the left ventricle. This consequently translates into a reduction in cardiac output and hemodynamic instability [8]. A PE-induced myocardial inflammatory response (*PE-induced myocarditis*) and oxygen imbalance can further contribute to a late hemodynamic instability [9].

The structural and functional differences between the right and left ventricle are easily brought out in case of PE [10]. Given its structure, the left ventricle well tolerates sudden increases in afterload. On the other hand, the RV is better suited to accommodate large increases in preload; however, it is not built to handle large and/or rapid increases in PAP. As a result of an increased afterload, the RV easily dilates,

and this will limit its ability to contract. At the same time, the bowling of the intraventricular septum, together with the high PVR consequent to PE, will limit the left ventricle preload. Being, the latter the weak point of the left ventricle function.

To counteract failure, in case of acute and sudden surge in PAP, the RV responds increasing the systolic inotropic adaptation, described by the Anrep law of the heart. In case of chronic increase in PAP, the RV will chronically implement the dimensional adaptation to preserve flow output. This is described by Starling's law of the heart.

The last European Guidelines for diagnosis and management of pulmonary hypertension have been developed by a joint taskforce including the European Society of Cardiology in collaboration with the European Respiratory Society in 2022 [11].

25.3 Diagnostics

The physical examination and clinical history are always the first diagnostic step in case of suspected PE. However, clinical signs are variable and often nonspecific, ranging from a completely asymptomatic to an unstable and life-threatening clinical presentation. Hence, as clinical judgment lacks standardization, several explicit clinical prediction rules have been developed.

25.3.1 Electrocardiography

Electrocardiography (ECG) is one of the most common and essential diagnostic tool for evaluating patients with unspecific clinical signs as chest pain and dyspnea. Several electrocardiographic changes can be suggestive of PE, however, not univocally related to PE. Hence, a pathologic ECG can help increasing suspicion of PE, but not confirming diagnosis. Among the most common pathological ECG findings related to PE, there are sinus tachycardia, T-wave inversion in the right pre-cordial leads, and the S1Q3T3 pattern.

25.3.2 Laboratory Biomarkers

B-type natriuretic peptides and *cardiac troponin* have high sensitivity for the early detection of RV failure and myocardial injury in patients with acute PE.

D-dimers derive from a simultaneous activation of coagulation and fibrinolysis and its specificity decrease with age. The negative predictive value of D-dimer testing is very high; hence a low value excludes the diagnosis of PE (class of recommendation: I). On the other hand, its specificity is very low (low positive predictive value of elevated D-dimer levels); hence D-dimer testing is not useful for confirming PE. Given the inverse relation between D-dimer specificity and patient's age, an age-adjusted cut-off improves the sensibility of high D-dimer in the elderly (class of recommendation: IIa) [7].

25.3.3 Echocardiography

An early and repeated bedside focused echocardiography is nowadays a first-line diagnostic test in the assessment of RV function and load. The use of echocardiography for the diagnosis of PE is strongly recommended (class of recommendation: I) [7]. However, it is important to point out that the echocardiographic evidence of RV overload is highly supportive, but not diagnostic, of PE. Among the echocardiographic findings, the most common and relevant ones are the following:

- Impaired right ventricular function (e.g., tricuspid annular plane systolic excursion—TAPSE—lower than 1.7 cm)
- Increased right-ventricle/left-ventricle end-diastolic diameter ratio
- Regional hypokinesia (McConnell's sign: with an akinetic mid RV free wall segment and spared apical contractility)
- Septal shift toward left with a D-shaped left ventricle and a paradoxical septal motion
- Tricuspid regurgitation with peak systolic velocity higher than 2.8–3.5 m/s
- Thrombi detectable in the right-heart or in the proximal pulmonary arteries

25.3.4 Computed Tomographic Pulmonary Angiography (CTPA)

CTPA is the gold standard and method of choice for the diagnosis of PE (class of recommendation: I) [7], allowing a good visualization of the whole pulmonary vasculature with a high sensitivity (83%) and specificity (96%).

25.3.5 Lung Scintigraphy

In this case, perfusion scans are combined with ventilation studies. Being a lower-radiation and contrast medium-sparing procedure, this specific technique with ventilation/perfusion (V/Q) scan may preferentially be applied in specific patients' populations such as pregnant women or in patients with renal failure or known allergies to contrast medium.

Other new CT-based lung imaging techniques such as single-photon emission CT (SPECT) and dual energy CT (DECT) have shown promising results and are more and more used for the diagnosis of PE [12].

25.3.6 Pulmonary Angiography

Before the introduction of CTPA, pulmonary angiography has been the gold standard technique for the diagnosis of PE. The advantage with pulmonary angiography is that the diagnosis is based on direct evidence of a thrombus in the pulmonary vasculature.

25.3.7 Cardiac Magnetic Resonance Imaging (cMRI)

cMRI reproducibly assesses atrial and ventricular size and morphology. In addition, cMRI can provide functional images, measuring blood flow in the pulmonary artery, aorta, and vena cava (see a practical example of cMRI to diagnose PE in the clinical case described in ▶ Chap. 27).

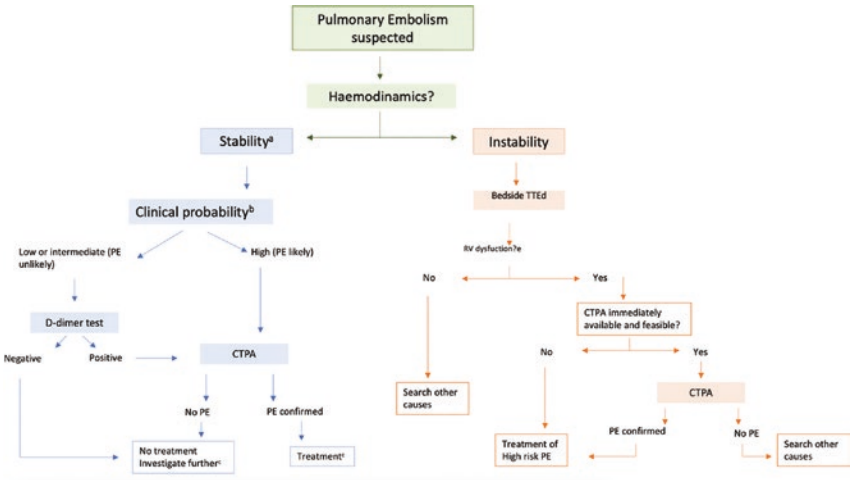
25.3.8 Pulmonary Artery Catheter

Invasive hemodynamic assessment is recommended in critical or therapy-resistant cases. The use of the pulmonary catheter for the assessment of the right-heart function and pulmonary hypertension is limited to the ICU setting, and it provides continuous valuable information about right and left atrial pressure, cardiac output, and pulmonary vascular resistance.

25.3.9 Compression Ultrasonography (CUS)

Lower-limb CUS has a sensitivity >90% and a specificity of around 95% for proximal symptomatic DVT. For the diagnosis of PE, CUS is limited to a simple four-point examination that is located bilaterally located at the groin and popliteal fossa. The only validated diagnostic criterion for DVT is incomplete compressibility of the vein, which indicates the presence of a clot. Flow measurements are instead unreliable.

Two main diagnostic algorithms have been proposed for patients with suspected unstable PE with or without includes the following three diagnostic steps: (1) a clinical suspicion; (2) early transthoracic bedside echocardiography (for hemodynamically unstable patients) or D-dimers (for hemodynamically stable patients); and (3) CTPA (see ◘ Fig. 25.1).



◘ **Fig. 25.1** Diagnostic algorithm for patients with suspected high-risk PE presenting with or without hemodynamic instability [7]

25.4 Risk Stratification, Prognostication, and the Pulmonary Embolism Severity Index

In the setting of a patient with an already confirmed diagnosis of PE, the *Pulmonary Embolism Severity Index* (PESI) can be utilized for prognostic purposes and risk stratification [6]. The outcomes determined with the PESI are risk of mortality and severity of complications. In this case the criteria considered for patient stratification are as follows: male sex, cancer, chronic heart failure, lung disease, heart rate, blood pressure, body temperature, and peripheral saturation of oxygen. The classes of stratification range from 1 to 5, with 5 indicating a very high risk for mobility and mortality.

PE is defined as *severe* when more than 30–50% of the total cross-sectional area of the pulmonary arterial bed is occluded by thrombo-emboli. On the other hand, PE is defined as *unstable* when, independently from its magnitude, it causes hemodynamic instability. However, the absence of hemodynamic instability does not exclude right ventricle (RV) dysfunction and thus an elevated risk for a later onset of hemodynamic instability. In this regard, an early accurate assessment of the right heart function is important at patient admission. In case of acute PE, a regular echocardiographic assessment of RV function should be always performed, even in the presence of a low *Pulmonary Embolism Severity Index* [7].

Base on the stratification of risk, a risk-adjusted management strategy for acute pulmonary embolism can be applied (see Fig. 25.2).

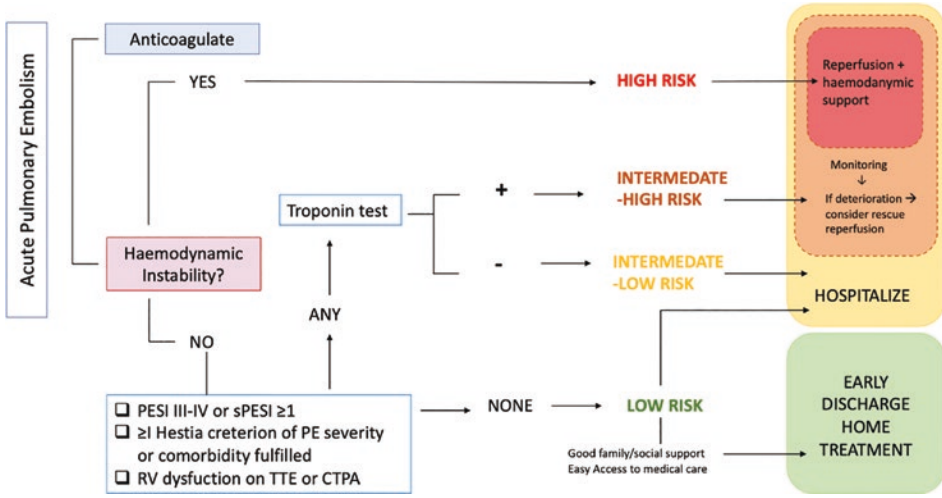


Fig. 25.2 Risk-adjusted management strategy for acute PE [7]

25.5 Management and Treatment of Acute PE

The initial approach to patients with suspected PE must focus upon stabilizing the patient while clinical evaluation and diagnostic testing are ongoing. The initial approach depends upon whether the patient is respiratory and hemodynamically stable or not. In case of hemodynamic instability and obstructive shock, with low arterial blood pressure requiring vasopressors, a very early management is required. Extremely unstable PE can lead to cardiac arrest. Resuscitation involves any combination of respiratory (oxygen, noninvasive or invasive mechanical ventilation) and hemodynamic (intravenous fluids, vasopressors) support. When contraindications to anticoagulation can be excluded, therapy with anticoagulants/thrombolytic/embolectomy should be promptly initiated even if the diagnosis of PE is not totally confirmed yet.

25.6 Management of Severe PE and RV Failure in the ICU Setting

1. *Acute Phase in Unstable Patients*
   Depending on the resources and expertise available in each hospital, a dedicated multidisciplinary pulmonary embolism team for the management of high-risk PE patients should be considered (class of recommendation: IIa) [7]. Rescue thrombolytic therapy is recommended for hemodynamic unstable patients (class of recommendation: I) [7]. Surgical embolectomy or catheter-directed treatment should be considered as alternatives to rescue thrombolytic therapy for patients who deteriorate hemodynamically (class of recommendation: IIa) [7]. Venous arterial extracorporeal circulation (VA-ECMO) may be considered in refractory circulatory collapse or cardiac arrest (see the clinical case described in ▶ Chap. 29).
2. *Counteract Severe Hypoxia and Hypercapnia*
   Hypoxemia is one of the most common features of severe PE and is mostly due to the mismatch between lung ventilation and perfusion (V/Q mismatch) and mainly to the increase in alveolar dead space (pathological dead space) where the affected areas of lung are ventilated but not perfused. Moreover, both hypoxia and hypercapnia should be avoided, since they promote pulmonary vasoconstriction and increase the afterload of the right ventricle. In case of refractory hypoxia despite continuous oxygen treatment, other oxygenation and ventilation techniques should also be considered, including high-flow nasal cannula and noninvasive or invasive mechanical ventilation.
3. *Management of Right Ventricle Failure*
   Acute PE is one of the most frequent causes of acute RV failure, and, on the other hand, RV failure is the principal determinant of early mortality in the acute phase of PE. Acute RV failure is a complex clinical syndrome, and a RV-protective management of acute PE has a central role in the clinical care of these patients [13]. The clinical case in ▶ Chap. 28 focuses on these RV-protective strategies. A RV-protective management of acute PE is composed of the following strategies:
   (a) Volume Optimization
   Aim: Optimization of RV preload.
   For this purpose, consider the right balance between volume loading and diuretics. RV failure patients may be preload-dependent, but an excessive vol-

ume loading has the potential to over-distend the RV and thereby increase failure.

(b) Pulmonary Vasodilation

Aim: Reduce pulmonary vasoconstriction, thus reducing RV afterload.

Pulmonary vasoconstriction during PE is a significant contributor to the increased right ventricular afterload and is often left untreated [14]. Vasoconstriction is induced locally by a complex interaction between humoral factors deriving from the activated platelets, endothelial effects, reflexes, and hypoxia. Vasoconstriction induced by serotonin, thromboxane, prostaglandins, and endothelin can be counterbalanced by vasodilators such as nitric oxide and prostacyclins. Exogenous administration of pulmonary vasodilators [15] in acute pulmonary embolism seems attractive, but this comes with a risk of systemic vasodilation and/or worsening of pulmonary ventilation-perfusion mismatch. Among others, inhaled NO (iNO) acts as a selective pulmonary agent, inducing vasodilatation in the ventilated regions of the lung. Phosphodiesterase-5 inhibitors (sildenafil), inhaled prostaglandin (iloprost), and hydralazine are other possible choices.

(c) Vasopressor and Inotrope Treatment

Aim: To optimize RV contractility as well as induce inodilation.

The use of vasopressors is often necessary, while waiting for the effects of pharmacological or surgical treatment. Several vasoactive drugs have been used to manage RV failure. Among others, the use of noradrenaline, milrinone, and levosimendan should be considered [16].

- *Noradrenaline*: noradrenaline is a vasoconstrictor but also a RV inotrope. Primarily acting on α1-receptors, noradrenaline increases systemic blood pressure, promotes positive ventricular interactions, and restores the coronary perfusion gradient. Noradrenaline has the advantage of not inducing the increase in vascular resistance at a pulmonary level. The secondary β1 effects on contractility have been shown to improve pulmonary artery/RV coupling. Noradrenaline should be limited in case of cardiogenic shock for potential effects of an increased afterload.
- *Milrinone*: A selective phosphodiesterase type III inhibitor that slows intracellular cAMP metabolism that can also improve inotropy and pulmonary vasodilatation. Milrinone is the agent of choice in causes of RV failure that differs from PE, being mostly used in patients with pulmonary hypertension from biventricular failure.
- *Levosimendan* is a calcium sensitizer that enhances myocardial contractility without increasing cytosolic calcium and oxygen demand. It has been increasingly used in patients with left heart failure but also demonstrated an improved RV function in patients with RV failure associated with chronic thromboembolic pulmonary hypertension. Although promising, from a pathohistological point of view, no clinical evidence of efficiency is available.
- In case of cardiogenic shock, inotropes such as dobutamine should be considered and as such is recommended in the current ESC guidelines [7]. However, dobutamine, as epinephrine, increases the risk of tachyarrhythmias and should be considered only when there is evidence of inadequate oxygen delivery despite the correction of abnormalities in RV preload, afterload, and ischemia.

(d) Mechanical Ventilation Strategy

In patients that require invasive mechanical ventilation, a protective ventilation strategy will be required to ameliorate gas exchange but also to control the potentially dangerous effects of a positive pressure ventilation on the right ventricle, preventing acute RV failure.

A RV-targeted protective mechanical ventilation [17] is characterized by:

- Low tidal volume
- Plateau pressure lower than 30 cmH_2O
- Moderate level of positive end-expiratory pressure (PEEP), optimized to reach the best balance between RV preload (that would benefit from a lower PEEP) and lung recruitment reducing PVR and afterload (which would benefit from a higher PEEP)
- Limit transpulmonary pressure
- Avoid intrinsic PEEP
- Apply prone positioning when possible
- Given the benefit of a lower PEEP, consider prone positioning for reaching a satisfactory lung recruitment at moderate PEEP levels, maintain a low transpulmonary pressure gradient, and favor the RV preload over afterload. How this strategy may alter prognosis in severe PE with RV failure remains to be evaluated [18].

(e) Mechanical Circulatory Support

Mechanical circulatory support with extracorporeal life support (ECLS), such as VA-ECMO, is a possible treatment option in the context of PE for a short-term rapid support, as bridge to diagnosis or bridge to treatment. See the clinical case reported in ▶ Chap. 29.

Mechanical circulatory support has become an established bridging tool to transplantation in patients with irreversible right heart failure, and it is occasionally used as a bridge to recovery in patients with reversible causes. However, the evidence supporting the use of VA-ECMO as a rescue therapy in the context of PE is poor and mainly suggests VA-ECMO as a bridge to mechanical thrombectomy.

25.7 Management of PE Outside from ICU Settings

25.7.1 Acute Phase in Stable Patients

Oral anticoagulation with non-vitamin K antagonist oral anticoagulant (NOAC: e.g., apixaban dabigatran, edoxaban or rivaroxaban) is the recommended treatment.

25.7.2 Chronic Treatment, Prevention of Recurrence, and Follow-Up

The treatment time with anticoagulation will be defined based upon the underlying disease and the risk stratification of each patient. Indefinite treatment with a vitamin-K antagonists (VKA) is recommended for patients with antiphospholipid anti-

body (class of recommendation: I) [7]. Extended anticoagulation should be considered for patients with persistent or transient/reversible risk factors (class of recommendation: IIa) [7]. Routine clinical evaluation is recommended 3–6 months after acute PE (class of recommendation: I) [7].

Take-Home Messages

- PE has a high incidence on the world population and is often fatal.
- The diagnostic options have been expanding nowadays and a multidisciplinary evaluation of severe PE cases is advantageous for an effective diagnostic and therapeutic process. Diagnostic algorithms can guide diagnosis and early treatment in case of suspicion of PE.
- Risk factors for PE are well known and classified. For a standardized clinical evaluation, they are organized in clinical prediction rules.
- Risk stratification for long-term prognosis is important once the diagnosis of PE is confirmed. A risk-adjusted management strategy has been proposed.
- The weak link in PE pathophysiology is the right heart. Right ventricle (RV) failure can have an early or late onset. The latter being probably related more to a secondary inflammatory reaction at myocardial level (*PE-induced myocarditis*).
- Echocardiography has changed the diagnostics process and timing to diagnosis in PE and must be performed in an early phase of PE suspicion and repeated during the evolution of the clinical case.
- The initial approach to severe PE focuses on respiratory and hemodynamic stabilization. Subsequently, the treatment strategy is centered on the management of RV failure. A RV-centered treatment of severe cases of PE is central for a successful treatment of severe PE.
- VA-ECMO is a rescue therapy in severe PE and can be used as bridge-to-treatment, to facilitate mechanical thrombectomy.

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Diagnosis of Pulmonary Embolism: An Uncommon Cause of Pulmonary Embolism

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Contents

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Learning Objectives

- Know the different diagnostic tools available and which are more efficient in detecting a pulmonary embolism.
- Know the most frequent symptoms and differential diagnosis of pulmonary embolism.
- Know infrequent causes of pulmonary embolism.
- Take into account medical history, occupation, and origin of the patients in order to make an accurate diagnosis.
- Know that imaging is critical for the diagnosis of PE and multivisceral echinococcosis, especially in cases of atypical localization.

26.1 Introduction

Pulmonary embolism (PE) is the third most common cardiovascular disease after acute coronary syndrome and stroke [1]. Advances in the last three decades in management of patients with suspected pulmonary embolism (PE) have improved diagnostic accuracy thanks to the creation of diagnostic algorithms (Fig. 26.1) based on the assessment of clinical pretest probability, D-dimer measurement, and imaging tests, mainly computed tomography pulmonary angiography (CTPA) (Table 26.1). These diagnostic algorithms allow a safe and cost-effective diagnosis for most patients with suspected PE, due to a non-negligible radiation dose and expensiveness of confirmatory imaging tests such as CTPA or ventilation-perfusion (V/Q) scans.

Hydatid disease, hydatidosis, or cystic echinococcosis (CE) is a universally distributed parasitosis caused by the larva of the cestode *Echinococcus granulosus*,

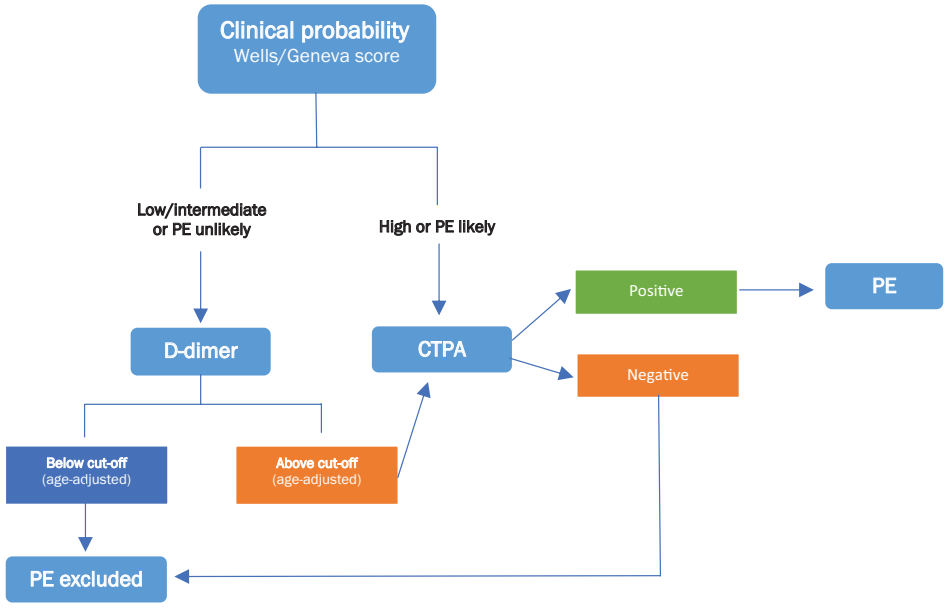

Fig. 26.1 Diagnostic algorithm of pulmonary embolism. Abbreviations: *CTPA* computed tomography pulmonary angiography, *PE* pulmonary embolism. (Adapted from *Righini* et al. [1])

Table 26.1 Investigations for PE diagnosis

Clinical probability—prediction rules for PE	• Wells score (previous PE or deep vein thrombosis—DVT, surgery or immobilization within the past 4 weeks, cancer, haemoptysis, heart rate > 100 bpm, clinical signs of DVT, alternative diagnosis less likely than PE) • Geneva score (age > 65 years, previous deep vein thrombosis or PE, surgery or fracture within 1 month, active malignancy, unilateral lower limb pain, haemoptysis, heart rate, pain on lower limb deep vein palpation and unilateral oedema) ** Should only be used after a suspicion of PE has been raised after clinical assessment of the patient*
D-dimer test	• Plasma D-dimer is a degradation product of cross-linked fibrin • Rise in presence of an acute clot • Exclusion test. D-dimer is not useful for confirming PE, is not specific ** Clinical probability and D-dimer are used in most diagnostic strategies as a first filter, in order to avoid thoracic imaging*
Echocardiography	• Sensitivity of 60% to 70% for diagnosis of PE • Identify indirect data of PE (RV dilatation, pulmonary arterial hypertension, etc.) ** It is not useful as a diagnostic study but it has an important role in the prognosis of PE and in case of instability haemodynamics*
Computed tomography pulmonary angiography	• **Gold standard nowadays** • Allows direct visualization of pulmonary arteries after intravenous injection of iodinated contrast medium • Excellent accuracy, wide availability, fast turnaround time, good spatial resolution and multi-planar reconstruction capabilities
Compression ultrasonography of lower limb veins	• Main diagnostic tool for DVT • The presence of a proximal DVT is highly predictive of PE • Sensitivity of 41% and a specificity of 96%
Ventilation-perfusion (VQ) scans	• Non-invasive technique allowing an indirect diagnosis of PE (perfusion defect with normal ventilation) • Can be used as an alternative imaging technique for diagnosing PE in those where CTPA is contraindicated • High negative predictive value. A positive predictive value of a high probability V/Q scan is approximately 90% • Major limitation: high proportion of non-diagnostic results (around 50%) and the inability to provide alternative diagnosis
Cardiac MRI	• Valuable alternative in patients with contraindications to iodinated contrast and in pregnant or young patients • The bright blood signal allows detection of pulmonary emboli even without intravenous contrast material • Sensitivity 78% and specificity 99% of contrast-enhanced MR angiography for detecting acute PE • Major limitation: large number of technically inadequate studies (25% of patients), cost, availability ** Should only be considered at **institutions routinely performing MRA** and routinely achieving **good diagnostic quality** and **only in patients with contraindications to CTPA***
Catheter pulmonary angiography	• Has been replaced by CTPA as the gold standard for the diagnosis of acute PE • Patients in whom endovascular treatment is being considered

whose definitive host is the dog. Humans are an accidental intermediate host for this parasite and are normally infected by the ingestion of food or water contaminated by the faeces of parasitized dogs. The molecular study of mitochondrial DNA makes it possible to distinguish up to ten different genotypes of *E. granulosus*. The most frequent is G1, which is related to infection in sheep. It is an important socioeconomic and public health problem in many low- and middle-income countries. It is estimated that this disease affects two to three million people worldwide [2], and Spain is among the European countries with the highest incidence of the disease in humans.

CE can affect any part of the human body, no matter what organ, tissue, or cavity. The most frequently affected organ is the liver (70–80%), and the lungs (10–30%) are the second most frequent location [3]. Multivisceral echinococcosis is defined by the simultaneous localization of hydatid cysts in more than one organ. This must be differentiated from multiple echinococcosis, which is defined as the localization of multiple hydatid cysts in the same organ. Cardiac involvement is very rare, occurring in 0.5–2% of patients, whose myocardium is invaded through the coronary circulation [4]. The left ventricle is the most frequent cardiac localization (55–60%), followed by the right ventricle with an incidence of 15%, interventricular septum (5–9%), left atrium (8%), pericardium (8%), pulmonary arteries (7%), and the right atrium (3–4%).

CE is usually a silent disease, and the signs and symptoms may be caused by the mass effect of the cyst, its superinfection, or anaphylactic reactions secondary to its rupture. The diagnosis is usually made in adulthood, through the clinical presentation, imaging tests, and/or serological determination. In this context, imaging is critical for the diagnosis of ME, especially in cases of atypical localization.

Occasionally, the hydatid cyst is detected incidentally on radiological or ultrasound studies performed for other reasons. In the lung, it may be identified on the chest X-ray as a rounded shadow of water density with well-defined boundaries. In the liver, a round image with calcium density may be seen if the cyst is fully or partially calcified, and abdominal ultrasound shows a rounded image, with wall reinforcement and echoes inside that reveal the presence of vesicles.

Suspecting that the tumour detected is a hydatid cyst, an analytical study should be carried out, especially in endemic areas when there are suggestive symptoms such as sudden urticaria with abdominal pain. It consists of a blood count and immunological tests (antibodies against the parasite) that will provide the biological diagnosis of CE. The blood count usually shows eosinophilia, and the immunological tests more specific and sensitive for the diagnosis are the indirect haemagglutination test and the ELISA test.

Treatment is based mainly on three pillars (◘ Table 26.2): antiparasitic drugs, surgery, and percutaneous drainage [2]. The choice of the most appropriate approach is based on the patient's symptoms and the characteristics of the cysts. The classic and main treatment for echinococcosis is surgery. The objective of surgical intervention is the elimination of both the parasite and the lesions it has produced. Only small, calcified cysts with negative biological tests can be managed without surgery. Those patients in whom there is a formal surgical contraindication will not be intervened either. However, medical treatment with albendazole, benzimidazole, or mebendazole can be effective perioperatively or between serial surgeries to sterilize the cyst and reduce the risk of anaphylaxis or recurrence.

Table 26.2 Treatment of cystic echinococcosis. Treatment of CE varies depending on the type, location, and number of cysts and whether the imaging results indicate that the cysts are active, transient, or inactive

Surgical intervention	Treatment of choice Objective: elimination of both the parasite and the lesions it has produced Cystoresection (can be closed or open): the ideal is to remove the entire cyst with its adventitial layer
Medical treatment	*Preoperative preparation and postoperative complement* **Albendazole** 400 mg/12 h. Daily dose for several months without surgery can cure 30% of small unilocular hydatid cysts. Treatment of choice for inoperable cysts. **Mebendazole** 40–50 mg/kg/day for several months (second option). ** Albendazole appears to be more effective than mebendazole due to its greater cyst penetration* *** Both drugs should not be administered in pregnancy and lactation* **** Long-term treatment with high doses of albendazole can cause bone marrow suppression and liver toxicity*
Percutaneous treatment of hydatid cysts	PAIR (puncture-aspiration of cyst contents—injection of hypertonic saline solution—reaspiration) ** There is a risk of allergic reaction during the cyst aspiration* *** Some studies showed that percutaneous drainage is as good as surgery in the management of uncomplicated hydatid cysts with fewer complications and shorter hospital stays*

Case Study

A 50-year-old Maghrebian man without known cardiovascular risk factors, who worked as a farmer, presented with chest pain and sudden dyspnoea to the Emergency Department. The patient had been diagnosed with ME with multiple complications in chronic treatment with albendazole and nitazoxanide. There was history of pulmonary cystectomy in his country of origin in his youth. He was urgently operated for peritonitis secondary to hepatic hydatid cyst rupture, performing splenectomy, resection of hepatic cyst and omentum in 2005. He was admitted in 2011 to cardiology due to chest pain, with cardiac magnetic resonance imaging (MRI) showing multiple pericardial and mediastinal cysts with coronary artery compression of the anterior descending artery that resolved spontaneously without complications. In 2016 he was admitted due to haemoptysis, and he was diagnosed with an endocavitary thrombus of hydatid origin in the right atrium (Fig. 26.2). In that time, it was decided, due to the high surgical risk and complexity, a watch and wait approach, and not undergoing surgery.

He consulted again in February 2019 due to chest pain and sudden dyspnoea while he was walking, without associated infectious symptoms the previous days. He went to a primary care centre where he was administered intravenous corticosteroids and bronchodilators without clinical improvement. Then, he was transferred to the Emergency Department of the regional hospital, where an ECG was performed, showing sinus tachycardia without significant alterations in repolarization.

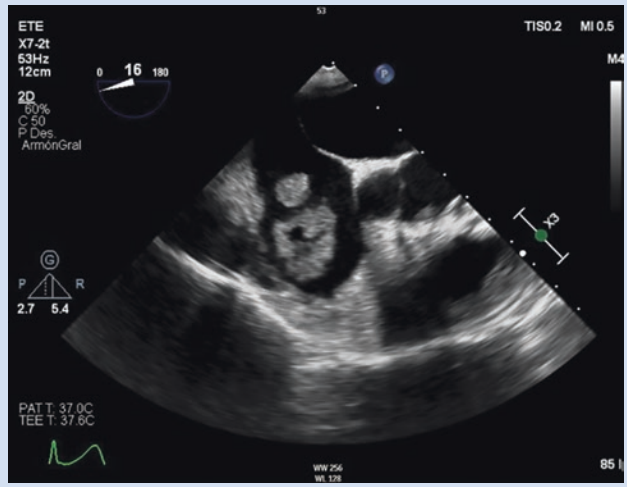

Fig. 26.2 Transesophageal echocardiography performed during the surgical procedure in which an intracavitary hydatid cyst is observed in the right atrium

Table 26.3 Differential diagnosis of our clinical case

Cardiac tumour	Many patients with a cardiac tumour are asymptomatic and for those patients that do have symptoms they are typically non-specific and similar to many other more common cardiovascular conditions Myxoma is a benign tumour of the heart and the most common primary heart tumour Heart can be metastasized by any malignant neoplasm (lung cancer, breast cancer, melanoma, renal cell cancer, and/or lymphoma are the most common neoplasms)
Infective endocarditis	Infection of the endothelium of the heart The clinical presentation is highly variable 25% of patients have evidence of embolic phenomena at presentation. Septic embolism is a severe complication of infective endocarditis
Acute pulmonary embolism	Most commonly originating from deep venous thrombosis of the legs The clinical presentation is variable and often nonspecific It is necessary evaluate risk factors and preclinical probability

Analytical determinations included elevated myocardial damage markers with troponin I values of 0.2 and 0.48 pg/mL and increased D-dimer (147,609 ng/mL). Suspecting a hydatid cyst complicated by pulmonary thromboembolism (Table 26.3), an urgent CTPA was performed (Fig. 26.3) which confirmed the diagnosis of PE of probable hydatid origin. After the diagnosis, the patient was transferred to the Intensive Care Unit (ICU) of a tertiary hospital.

The patient was admitted to the ICU haemodynamically stable, breathing spontaneously with RR 23 bpm with oxygen therapy using a Venturi-type mask with FiO2 45% and satO2 94%. During admission, it was not necessary to increase respi-

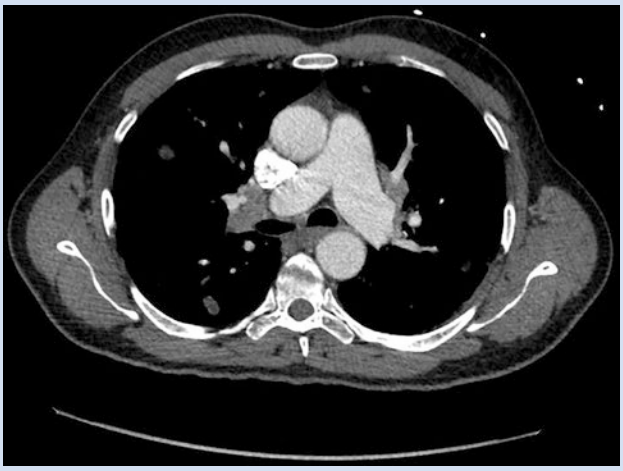

Fig. 26.3 Computed tomography pulmonary angiography. Multiple filling defects in lobar and segmental branches bilaterally in relation to pulmonary embolism of hydatid origin

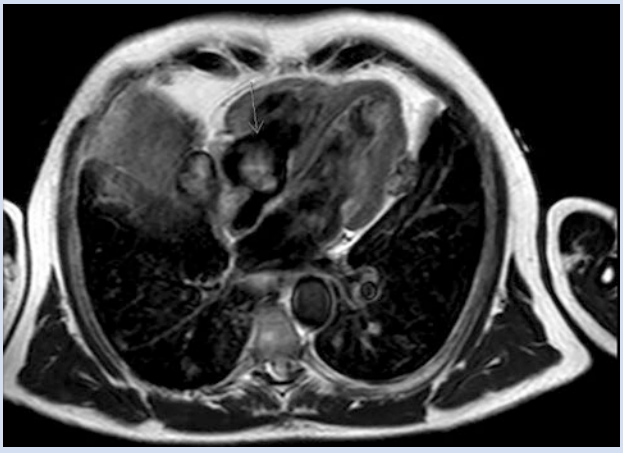

Fig. 26.4 Cardiac MRI. Pericardial multicystic lesion on the lateral side of the RA, infiltrating the cardiac chamber, with a lesional and intracavitary thrombotic component also of hydatid origin

ratory support. A new cardiac MRI was performed (Fig. 26.4) which showed an increase in the intracavitary component of the lesion in the lateral wall of the RA. Given these findings, the case was discussed in a medical-surgical session and was accepted for resection of the hydatid cyst in the RA. A scheduled surgery was performed by median sternotomy and extracorporeal circulation without complications, removing several cysts located at the level of the ascending aorta, aortopulmonary window, on the RA, and two endocavitary cysts anchored to the lateral wall of the RA.

The patient evolved favourably without presenting cardiovascular or respiratory complications, being discharged to his reference hospital after 31 days of admission.

26.2 Discussion

CE is a chronic parasitosis with a worldwide distribution and a higher prevalence in temperate zones, such as the Mediterranean region; it has endemic foci in all inhabited continents. Spain is among the European countries with the highest incidence of the disease in humans.

CE is usually a silent disease, and the signs and symptoms may appear when the disease has progressed. This case demonstrates the importance of finding out the previous medical history of our patients, as well as their origins and occupation, especially when they work with animals. It is relevant to rule out this disease in young patients in contact with farm animals or living in endemic areas with suspicious symptoms, including embolization as clinical presentation in patients without risk factors.

Although a microbiological diagnosis is mandatory, we should take into account that imaging is critical for the diagnosis of multivisceral echinococcosis, especially in cases of atypical localization.

The most appropriate treatment and its choice must be individualized and based on the patient's symptoms and the characteristics of the cyst. Patients with cardiac hydatidosis may develop acute life-threatening complications secondary to the invasion of surrounding cardiac structures, such as cyst rupture together with systemic and pulmonary dissemination. Therefore, surgical excision is the definitive method of treatment for cardiac hydatid cysts in order to prevent these potential lethal complications, even for asymptomatic patients. In other similar cases, surgical excision was the definitive and most suitable therapy for patients with cardiac hydatid cysts [4–6]. Accordingly, it is considered the treatment of choice for patients with cardiac involvement, especially in those with intracavitary dissemination of the cysts in the left and right heart cavities. Although surgical treatment was initially rejected, it finally proved to be the definitive and most appropriate treatment for our patient, given the multiple potentially fatal complications that he experienced throughout his evolution.

Take-Home Messages

- Diagnosis of pulmonary embolism can be challenging and easily missed due to the non-specific presenting symptoms, such as dyspnoea and pleuritic chest pain.
- Imaging plays an essential role in the diagnosis and management of acute PE.
- Computed tomography pulmonary angiography is the gold standard imaging modality for investigation of acute pulmonary embolism.
- Echocardiography is an important bedside imaging tool for the diagnosis of pulmonary embolism. It is a cheap, innocuous, non-invasive test for rapid diagnosis of pulmonary embolism and determining the degree of the risk category (high- or low-risk patients). In the hands of an expert operator, it can give us a lot of information, especially in the initial evaluation.
- Echocardiography can be useful for ruling in a pulmonary embolism but should not be the main test for ruling out a pulmonary embolism.
- Echocardiography findings of pulmonary embolism (Table 26.4) include McConnell's sign, enlarged RV, IVS flattening, and the 60/60 sign.
- Cystic echinococcosis is a universally distributed parasitosis that can affect any part of the human body, even multiple anatomic locations simultaneously. Multivisceral echinococcosis is defined by the simultaneous localization of hydatid cysts in more than one organ.
- Cystic echinococcosis is usually a silent disease, and the diagnosis is usually made in adulthood, through the signs and symptoms caused by the mass effect of the cyst, its superinfection, or anaphylactic reactions secondary to its rupture.
- Treatment of cystic echinococcosis is based mainly on three pillars: use of antiparasitic drugs, surgery, and percutaneous drainage. The choice of the most appropriate approach should be personalized, based on the patient's symptoms and the characteristics of the cysts.

Table 26.4 Echocardiography findings in pulmonary embolism

RV enlargement	27%	The increase in pulmonary vascular resistance results in increased RV afterload and increased RV wall tension
RV free wall hypokinesis	27%	The RV dilates acutely and can become dysfunctional
McConnell's sign	20%	Regional right ventricular wall motion disturbance: Hypokinesia of the basal and middle thirds of the RV free wall with preservation of its apex
Interventricular septal flattening	18%	As a result of pressure overload, the RV dilates and the interventricular septum flattens in systole
60/60 sign	13%	Time of tricuspid acceleration less than 60 ms in the presence of a tricuspid systolic gradient greater than 30 but less than 60 mmHg

Summary

The diagnosis of pulmonary embolism (PE) arises based on clinical suspicion, and it can be difficult due to the great variability in the form of presentation and the non-specific symptoms. The improvement of diagnostic strategies almost completely eliminated the need for invasive diagnostic testing, and nowadays non-invasive imaging techniques are crucial in the diagnosis and management.

Multivisceral echinococcosis (ME) is a rare entity that is defined by the simultaneous presence of hydatid cysts in more than one organ. We present a rare cause of PE in a patient with ME as an infrequent complication of this disease in uncommon anatomical locations, such as the heart. Although surgical treatment was initially dismissed, it finally proved to be the definitive and most appropriate treatment for this patient, given the multiple potentially life-threatening complications that he experienced throughout his evolution. The clinical manifestations of cardiac cystic echinococcosis (CE) are highly variable and depend on the size, number, and location of the cysts. Early diagnosis and definitive treatment are important to prevent fatal complications.

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Right Ventricular Failure in Pulmonary Embolism: The Forgotten Chamber—When in Trouble, Go Back to Basics

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Learning Objectives

- Understanding the pathophysiology in acute right ventricular (RV) failure
- Understanding the mechanisms of acute RV failure: abnormal preload, reduced contractility, increased afterload and altered ventricular interdependence, and how these contribute to the spiral of death
- Knowing the common causes of acute RV failure and how to diagnose them
- Applying the knowledge of RV physiology in the management of acute RV failure, with the focus on optimising RV preload, contractility and afterload
- Knowing how to interpret pulmonary artery catheter-derived haemodynamic parameters

27.1 Introduction

Acute right ventricular failure is not uncommonly encountered in the intensive care unit (ICU). Causes include acute pulmonary embolism (PE), acute respiratory distress syndrome (ARDS), right ventricular infarction and acute decompensation of chronic pulmonary hypertension. The right ventricle (RV) has received little attention in the past, with most cardiac assessments and therapeutics focusing on the left ventricle (LV). As the RV is a unique chamber with distinct anatomy and physiology, coupled to the systemic venous return and the pulmonary circulation, it precludes direct extrapolation of LV pathophysiology to the RV. Management of RV failure remains challenging with a high mortality rate. We present a case of RV failure from massive PE and outline its management based on cardiovascular physiological principles with advanced haemodynamic monitoring using pulmonary artery catheter (PAC) to achieve successful resolution of RV dysfunction.

Case Presentation

A 65-year-old female presented to the emergency department with drowsiness, fever, shortness of breath and chest discomfort for 2 days. There were no gastrointestinal or urinary symptoms. She had no recent travel history or sick contacts. Significant past medical history included diabetes mellitus, hyperlipidaemia and schizophrenia.

On examination, she was febrile (temperature 39.4 °C), blood pressure (BP) was 99/62 mmHg, heart rate (HR) was 147/min, respiratory rate (RR) was 34/min, and oxygen saturation (SpO_2) was 95% on room air. There were bibasal crepitations on auscultation of the lungs. She was lethargic but rousable and withdrew to pain stimuli. There were no focal neurological deficits. She had pressure sores over her back and sacrum with no erythema or fluctuance. There was no lower limb oedema. Examination of the cardiovascular and abdominal systems was normal.

Further history from her brother, who was her primary caretaker, revealed functional decline after a fall 1 month before, and she had remained mostly chairbound after.

27.2 Investigations

The following laboratory tests were obtained: white cell count 7.5 × 10^9/L; haemoglobin 14.0 g/dL; platelets 249 × 10^9/L; urea 18.6 mmol/L; creatinine 101 μmol/L (baseline 37 μmol/L); sodium 140 mmol/L; potassium 3.0 mmol/L; and chloride 102 mmol/L. Arterial blood gas on fraction of inspired oxygen (FiO_2) of 0.27 revealed: pH 7.45; partial pressure of carbon dioxide ($PaCO_2$) 22 mmHg; partial pressure of oxygen (PaO_2) 62 mmHg; bicarbonate 15 mmol/L; and base excess −9. Lactate was elevated at 2.8 mmol/L. Serum beta-hydroxybutyrate was 3.4 mmol/L, with a raised glucose of 26.8 mmol/L and serum osmolality of 327 mmol/kg. Inflammatory markers were also elevated, with C-reactive protein of 339.6 mg/L and procalcitonin of 10.36 μg/L. Liver function tests were normal. High sensitive troponin I was raised to 84 ng/L (reference 0–18 ng/L). Point-of-care ultrasound (POCUS) in the emergency department showed collapsible inferior vena cava (IVC), with a preserved LV ejection fraction and a normal sized RV. Chest X-ray showed patchy airspace opacities in bilateral lower zones. Computed tomography (CT) scan of the brain did not reveal acute intracranial haemorrhage or territorial infarct.

She was admitted to the high dependency unit for septic shock secondary to pneumonia, complicated by acute kidney injury, diabetic ketoacidosis (DKA) and type 2 myocardial infarction. Despite 4 L of intravenous (IV) crystalloids (1 L of 0.9% sodium chloride and 3 L of plasmalyte), she remained hypotensive and was started on noradrenaline. She was also commenced on IV insulin for DKA and IV piperacillin/tazobactam for pneumonia.

As her condition deteriorated with worsening hypoxaemia, hypotension and metabolic acidosis, she was transferred to ICU the next day. She was intubated and placed on mechanical ventilation with the following settings: pressure-regulated volume control mode; tidal volume 375 ml (predicted body weight of 41 kg); RR 22/min; positive end-expiratory pressure (PEEP) 8 cmH_2O; FiO_2 0.5; and achieving a PaO_2/FiO_2 (PF) ratio of 300 mmHg. However, her hypotension worsened requiring rapidly escalating doses of vasopressors (noradrenaline 0.4 μg/kg/min and vasopressin 2.4 units/h).

27.3 Differential Diagnosis

Differential diagnoses for worsening hypotension include vasodilatory shock from sepsis and sedation, hypovolaemic shock, cardiogenic shock, obstructive shock or a combination of these. POCUS is a useful bedside tool that can be done rapidly to distinguish amongst the different types of shock. POCUS revealed RV dilatation and severely impaired RV systolic function with a tricuspid annular plane systolic excursion (TAPSE) of 11 mm. There was also diastolic flattening of the interventricular septum, indicative of RV volume overload, which reduced the LV compliance and LV diastolic filling. IVC was dilated with minimal variability with respiration. These features were consistent with acute RV failure. There was no pericardial effusion or absence of lung sliding to suggest obstructive shock from cardiac tamponade or tension pneumothorax.

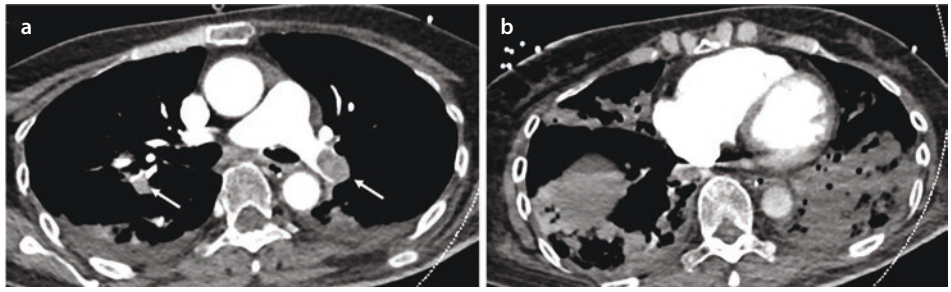

Fig. 27.1 Computed tomography pulmonary angiogram (CTPA) confirmed the diagnosis of pulmonary embolism. a Filling defects were seen in the left main pulmonary artery and right segmental pulmonary artery (arrows). b The right ventricle (RV):left ventricle (LV) ratio was >1 with straightening of the interventricular septum, suggestive of RV strain. There was also bilateral lower lobe consolidation

Causes of acute RV failure include PE, acute *cor pulmonale* from ARDS and RV infarction. An urgent CT pulmonary angiogram (CTPA) confirmed the diagnosis of PE involving the left main pulmonary artery (PA), left upper and lower lobar pulmonary arteries as well as segmental branches to the bilateral upper and lower lobes and right middle lobe. The RV:LV ratio was >1 and there was flattening of the interventricular septum, consistent with the POCUS findings (Fig. 27.1). Acute *cor pulmonale* from ARDS was another important consideration given her severe bilateral lower lobe pneumonia. However, her PF ratio was 300 mmHg post-intubation and her lung compliance was fairly preserved at 57 mL/cmH_2O. Repeat ECG did not reveal any acute ischaemic changes to suggest RV infarction.

27.4 Treatment

She received definitive therapy for high-risk (massive) PE with systemic thrombolysis using recombinant tissue plasminogen activator, followed by anticoagulation with IV unfractionated heparin. However, she remained hypotensive on noradrenaline 0.9 μg/kg/min, vasopressin 2.4 units/h and adrenaline 0.38 μg/kg/min.

Pulmonary artery catheter (PAC) was inserted to guide haemodynamic management. The following measurements were obtained: pulmonary artery pressure (PAP) 25/17 mmHg (mean 21); cardiac index (CI) 2.4 L/min/m^2; stroke volume index (SVI) 16 mL/m^2; systemic vascular resistance index (SVRI) 2146 dynes-sec/cm^{-5}/m^2; right ventricular end diastolic volume index (EDVI) 127 mL/m^2; RV ejection fraction (RVEF) 12%; and mixed venous oxygen saturation (SvO_2) 75% (Table 27.1).

She was diagnosed with severe RV failure causing significant RV volume overload, which compromised LV diastolic filling (from ventricular interdependence), leading to cardiogenic shock. There was also increased RV afterload from high pulmonary vascular resistance (PVR) secondary to PE, positive pressure ventilation and high dose vasopressors. As she was not a candidate for extracorporeal membrane oxygenation (ECMO), further management was largely supportive to optimise the RV preload, contractility and afterload.

Table 27.1 Haemodynamic status, pulmonary artery catheter measurements and treatment summary in ICU

Day of ICU	1	2	3	4	5	6	7	8	9	10	11	12
Vital signs												
SBP/DBP (MAP), mmHg	75/57 (65)	116/53 (66)	120/68 (87)	88/53 (66)	133/76 (97)	114/67 (83)	113/64 (82)	120/61 (83)	117/59 (80)	116/65 (85)	95/56 (71)	127/64 (88)
HR, bpm	143	152	138	113	114	112	113	97	93	102	96	86
SpO_2, %	100	96	96	99	99	100	98	97	98	94	97	94
Pulmonary artery catheter haemodynamic measurements												
PAP (mean PAP), mmHg	–	25/17 (21)	27/12 (18)	26/10 (17)	29/14 (19)	28/13 (18)	33/16 (22)	33/14 (21)	32/11 (18)	31/12 (20)	38/16 (24)	32/14 (20)
CI, L/min/m^2	–	2.4	2.7	2.6	2.7	2.9	3.1	3.3	2.8	3.3	3.7	3.3
SVI, mL/m^2	–	16	19	24	24	26	29	32	33	33	37	38
SVRI, dyn-s/cm^{-5}/m^2	–	2146	2526	2423	1995	2112	2601	2112	2032	1656	1166	1512
EDVI, mL/m^2	–	127	127	139	123	110	111	115	110	102	99	113
RVEF, %	–	12	14	17	19	23	26	28	30	31	37	34
SvO_2, %	–	75	61	55	56	60	67	54[a]	58[a]	70	68	64
PAOP, mmHg	–	–	–	–	–	–	6	–	6	–	–	6
PVRI, dyn-s/cm^{-5}/m^2	–	–	–	–	–	–	400	–	328	–	–	304
Vasopressors/inotropes												

(continued)

Table 27.1 (continued)

Day of ICU	1	2	3	4	5	6	7	8	9	10	11	12
Noradrenaline, μg/kg/min	0.60	1	1	0.72	0.48	0.40	0.26	0.28	0.05	0.20	0.20	0.15
Vasopressin, units/h	2.4	2.4	2.4	2.4	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Adrenaline, μg/kg/min	0.35	0.38	0	0	0	0	0	0	0	0	0	0
Milrinone, μg/kg/min	–	0.125	0.125	0.25	0.25	0.375	0.375	0.375	0.375	0	0	0
Levosimendan, μg/kg/min	–	–	–	–	–	–	–	–	–	0.10	0.15	0.15
Esmolol, μg/kg/min	–	–	12.5	25	25	25	25	25	25	25	25	25
Pulmonary vasodilators												
Iloprost	–	10 mcg Q4H	10 mcg Q4H	10 mcg Q4H	20 mcg Q4H	20 mcg Q4H	20 mcg Q4H	20 mcg Q4H	20 mcg Q4H	10 mcg Q4H	10 mcg Q6H	10 mcg Q8H
Sildenafil	–	–	–	–	–	–	–	–	–	25 mg TDS	50 mg TDS	50 mg TDS
Fluid management												

Aquapheresis ultrafiltration, mL/day	–	50	400	600	700	370[b]	0[b]	0[b]	500	800	700	0
Net balance, mL/day	+635	+1936	+1058	+881	+362	+696	+1106	+950	+730	−201	+651	+999

bpm beats per minute; *CI* cardiac index; *DBP* diastolic blood pressure; *EDVI* end diastolic volume index; *HR* heart rate; *MAP* mean arterial pressure; *PAP* pulmonary artery pressure; *PAOP* pulmonary artery occlusion pressure; *PVRI* pulmonary vascular resistance index; *RVEF* right ventricle ejection fraction; *SBP* systolic blood pressure; SpO_2 peripheral oxygen saturation; *SVI* stroke volume index; SvO_2 mixed venous oxygen saturation; *SVRI* systemic vascular resistance index

[a] Patient had bloody oropharyngeal secretions with haemoglobin drop from 7.9 g/dL to 6.4 g/dL, which explained the decrease in SvO_2. SvO_2 improved after packed red blood cell transfusion

[b] Aquapheresis was stopped for 72 h due to vascular access issues. Patient was started on IV frusemide infusion 10–30 mg/h in the interim

To reduce RV volume overload (and optimise RV preload), she had controlled fluid removal with aquapheresis. The blood flow rate was set at 40 mL/min, and ultrafiltration flow rate was set low at 10–30 mL/h to allow gradual volume removal, without inducing haemodynamic instability. EDVI, a marker of RV preload, showed a decreasing trend over time, with an associated improvement in LV stroke volume index (SVI), suggesting improved LV diastolic filling as RV volume overload reduced (Table 27.1).

To improve RV contractility, she was started on IV milrinone at 0.125 μg/kg/min (which also had pulmonary vasodilatory effect and helped to reduce RV afterload), and the dose was titrated upwards to 0.375 μg/kg/min. RVEF, SVI and CI showed increasing trend over time (Table 27.1).

To reduce RV afterload, she was kept on low level of PEEP of 5 cmH_2O, and ABG was monitored closely to avoid hypoxaemia and hypercapnia, which may increase the pulmonary vascular resistance (PVR). Vasopressor doses were gradually reduced. She was also started on inhaled iloprost, which is a pulmonary vasodilator. Pulmonary vascular resistance index (PVRI), a marker of RV afterload, showed a decreasing trend over time (Table 27.1).

Additionally, IV esmolol was started to reduce tachycardia, in order to improve LV diastolic filling and stroke volume, and ionised calcium was corrected to target a level of >1.2 mmol/L.

27.5 Evolution, Outcome and Follow-Up

Her haemodynamics improved with optimisation of RV preload, contractility and afterload. Transthoracic echocardiogram on day 12 of ICU admission showed normalisation of RV size and function (Fig. 27.2).

IV milrinone was transited to IV levosimendan while inhaled iloprost was transited to oral sildenafil. She was extubated on day 17 of ICU stay. However, she developed ventilator-associated pneumonia and was re-intubated 1 day after and demised from respiratory failure 24 days from the initial presentation.

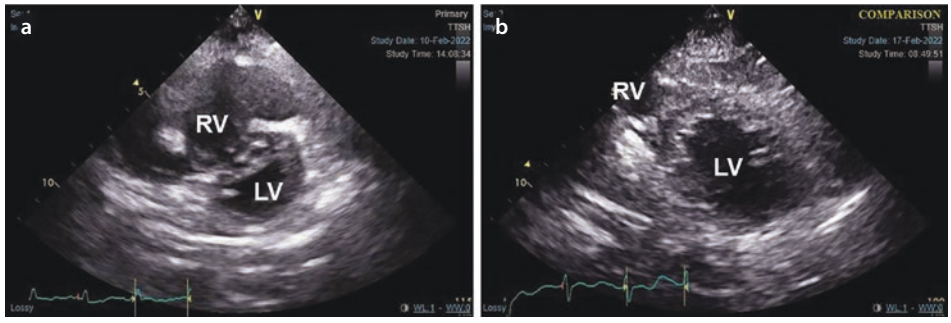

Fig. 27.2 Parasternal short axis view of transthoracic echocardiogram (TTE) performed on day 5 a and day 12 b of intensive care unit stay. a TTE on day 5 showed a severely dilated right ventricle (RV) with flattening of the interventricular septum and compression of the left ventricle (LV). b TTE on day 12 showed normalisation of RV and LV sizes

27.6 Discussion

This case highlights the need for a high index of suspicion for acute RV failure in a patient with worsening hypotension post-intubation. Acute RV failure can be easily missed if not actively sought out, and the diagnosis typically relies on echocardiogram. In this case, the cause of acute RV failure was massive PE. It is imperative to look for PE as definitive treatment involves reperfusion therapy with thrombolysis (if no contraindication), followed by anticoagulation. Beyond that, supportive management in ICU involves optimisation of RV preload, contractility and afterload to prevent the spiral of death in RV failure [1]. PAC plays an important role here as it allows continuous assessment of RV function, which cannot be achieved using transpulmonary thermodilution or pulse contour analysis.

Preload optimisation involves judicious fluid management—not too little as a higher mean systemic filling pressure is required to overcome the elevated right atrial pressure to drive venous return; yet not too much as RV over-distension alters the contractile function of myocardium and, by ventricular interdependence, results in a drop in LV filling and LV stroke volume (SV). Gentle diuresis may help to improve haemodynamics when the RV is dilated. In our patient, we used aquapheresis, which unlike loop diuretics, has the advantage of removing isotonic plasma water at a precise rate, without affecting the concentration of other electrolytes [2].

For contractility optimisation, inotropes with pulmonary vasodilatory effects such as milrinone and levosimendan can be used. Kerbaul et al. demonstrated that levosimendan can improve RV-PA coupling by increasing RV contractility and reducing RV afterload in an experimental animal model of PE [3]. We managed to achieve good physiological effects with levosimendan, when transiting from milrinone.

Afterload optimisation involves "RV-protective" ventilatory strategy with low PEEP and avoidance of hypoxaemia and hypercapnia. In addition, pulmonary vasodilators such as inhaled nitric oxide, phosphodiesterase-5 inhibitors and prostaglandins have been attempted in acute PE, although their use is limited to case reports [4]. We used inhaled iloprost and sildenafil with positive haemodynamic effects.

Besides preload, contractility and afterload, another important but often overlooked determinant of SV is heart rate and rhythm. Tachycardia is a compensatory response to hypotension, in the attempt to increase cardiac output (CO). However, excessive tachycardia can have a paradoxical effect of worsening CO due to reduced LV diastolic filling time and coronary perfusion. Our patient had excessive tachycardia despite weaning of inotropes. The use of esmolol, though counterintuitive, improved her CO and MAP. Any tachyarrhythmias such as atrial fibrillation or flutter should also be treated to restore atrial contraction and atrioventricular synchrony [5].

Take-Home Messages

- Acute RV failure can be easily missed if not actively sought out, and the diagnosis typically relies on echocardiogram. Pulmonary artery catheter (PAC) has the advantage of continuous monitoring of RV function.
- A good understanding of cardiovascular physiology is essential in managing acute RV failure, with the focus on optimising RV preload, contractility and afterload.
- For preload optimisation, judicious fluid management is key as too much fluid may be harmful, especially when the RV is already dilated.
- For contractility optimisation, inotropes with pulmonary vasodilatory effects can improve RV-PA coupling.
- For afterload optimisation, "RV-protective" ventilatory strategies are crucial. Pulmonary vasodilators have an increasing role.
- Advanced therapeutic options with mechanical circulatory support should be considered early in appropriate patients.

27

Summary

The right ventricle (RV) has traditionally been given less attention but can be rapidly fatal when it fails. Management of acute RV failure in the ICU remains challenging with a high mortality rate. In this case, we demonstrated how a good understanding of cardiovascular physiology and its application in: (i) interpretation of PAC-derived haemodynamic parameters and (ii) selection of therapeutic strategies to optimise RV preload, contractility and afterload, achieved successful resolution of RV dysfunction. This is especially important when mechanical circulatory support device is not suitable or available.

Questions

1. What is the spiral of death in acute PE and RV failure?
2. How does positive pressure ventilation affect the RV?
3. What is the treatment of RV failure in acute PE?

Answers

1. In acute PE, there is an abrupt increase in RV afterload from thromboembolic occlusion of the pulmonary arterial bed, resulting in RV dilatation and leftward septal shift (ventricular interdependence). This impairs LV preload and LV cardiac output, leading to systemic hypotension. The excessive RV wall tension also causes neurohormonal activation, which increases RV oxygen demand. At the same time, RV oxygen supply is reduced due to impairment of coronary perfusion pressure, which is made worse by systemic hypotension, as most of the RV coronary blood flow occurs in systole. This demand-supply imbalance results in RV ischaemia and further reduction in RV contractility, hence further RV dilatation and LV diastolic and systolic dysfunction, spiralling into haemodynamic instability and death.
2. Positive pressure ventilation can reduce RV preload (by decreasing venous return) and increase RV afterload (by compressing intra-alveolar vessels and converting West zone 3 to West zone 1 and/or 2). These combined effects can worsen RV

stroke volume and precipitate cardiac arrest upon intubation and initiation of mechanical ventilation.

3. Definitive treatment for high-risk (massive) PE involves reperfusion therapy with thrombolysis (if no contraindication), followed by anticoagulation. Supportive treatment includes: (i) optimising RV preload with judicious fluid management; (ii) improving RV contractility using inotropes ideally with pulmonary vasodilatory effects; (iii) reducing RV afterload with "RV-protective" ventilatory strategies and the use of pulmonary vasodilators; (iv) avoiding excessive tachycardia and correcting tachyarrhythmias; and (v) mechanical circulatory support such as VA-ECMO.

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VA-ECMO for Resuscitation of Cardiac Arrest After Pulmonary Embolism in Brain Stem Intracranial Hemorrhage

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Contents

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Learning Objectives

- Multiprofessional approach to succeed in cardiac arrest in special circumstances
- Eligible ICU patients for extracorporeal CPR and VA-ECMO therapy in cardiac arrest in special circumstances
- ICU workflow associated with a favorable post-resuscitation outcome after prolonged CPR

28.1 Introduction

In cardiac arrest caused by an acute pulmonary embolism and not responding to advanced cardiac life support, administration of a fibrinolytic therapy and continuous CPR for 60–90 min is recommended [1]. This approach might be lethal in patients with a recent intracranial hemorrhage. Likewise, surgical embolectomy with cardiopulmonary bypass requiring significant systemic anticoagulation might lead to a devastating progress of the intracranial bleeding.

Case Presentation

A 50-year-old male with a history of epilepsy was admitted to the emergency room with sudden onset headache, a right-sided brachial hemiparesis, and significant dysphagia. Cranial computed tomography showed an acute brain stem intracranial hemorrhage ranging from the pons to the mesencephalon (Fig. 28.1). With a conservative, non-neurosurgical treatment approach, the patient was admitted to the intensive care unit (ICU). With worsening of dysphagia and diagnosis of community-acquired pneumonia and because of a further decline in the level of consciousness, the patient required endotracheal intubation and mechanical ventilation. Anti-infective therapy was consecutively started and adapted to microbiological findings. In addition, prolonged pulmonary weaning from mechanical ventilator was expected based on the current neuropathology with high degree dysphagia. Due to a difficult airway, early surgical tracheostomy was performed. On ICU day 4, the patient, weaned from all sedation, was fully awake and oriented with assisted spontaneous breathing on the ventilator with infectious situation under control and hemodynamically stable waiting for discharge to the next available place in an early neurorehabilitation facility. Thromboembolic prophylaxis occurred with continuous infusion of unfractionated heparin.

Around 4:30 a.m. of ICU day 5, the patient suffered a sudden cardiac arrest during a non-verbal communication with his nurse. Immediate high-quality CPR was started with manual chest compressions monitored by an arterial line in situ and controlled ventilation. Advanced cardiac life support was performed according to current guidelines. Heart rhythm monitoring on the electrocardiogram (ECG) showed a pulseless electric activity (PEA). Epinephrine was given through the central venous catheter in situ. When there was no return of spontaneous circulation (ROSC) after two cycles of CPR, the in-house consultant from anesthesia arrived at the bedside and the on-call senior attending ICU was called into hospital.

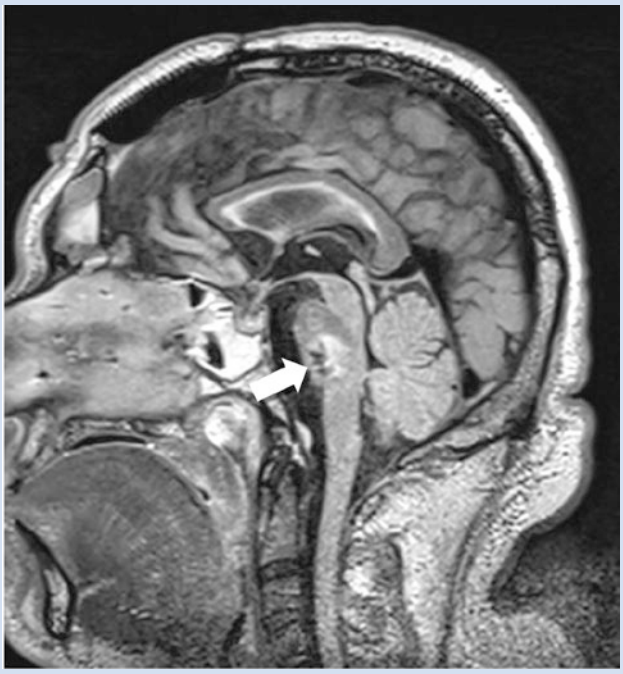

Fig. 28.1 Sagittal view of a cranial magnetic resonance imaging with a pontine intracranial hemorrhage (white arrow)

28.2 Investigations

With no ROSC and a continuing PEA, infusion of epinephrine was started according to current guidelines [1]. An arterial blood gas analysis was performed, and focused echocardiography of the thorax and heart were performed to narrow the spectrum of possible differential diagnoses of the acute cardiac arrest.

28.3 Differential Diagnosis

We based our differential diagnoses on the clinical setting, the history of the acute cardiac arrest, the clinical monitoring, and the findings of the rapidly performed arterial blood gas analysis. We did not find any electrolyte or biochemical disturbances, toxics, hypovolemia, or disturbances of body temperature that could explain the cardiac arrest. Thus, three potential causes of cardiac arrest remained plausible:

- Thrombotic: acute myocardial infarction/coronary thrombosis
- Thrombotic: acute pulmonary embolism
- Special: cardiac arrest associated with compression of brain stem by acute rebleeding of the brain stem intracranial hemorrhage [1]

A potential tension pneumothorax was rapidly excluded by bedside transthoracic ultrasonography with detection of a bilateral sufficient mobility of the pleura. Furthermore, pericardial tamponade was excluded by focused echocardiography. Echocardiography further showed a ballooning and resting right ventricle with a small, empty, and intermittently irregularly contracting left ventricle, placing acute right heart failure/arrest due to a pulmonary embolism on first place of the differential diagnosis for the reason for the acute cardiac arrest. In parallel to the clinical workup and the advanced cardiac life support, the on-call senior attending of neurosurgery was able to review the recent radiographic imaging by log-on to the digital database of cranial computed tomography and MRI scans from home. In a bedside multidisciplinary telephone conference, an acute rebleeding of the brain stem intracranial hemorrhage could have been a likely diagnosis for the cardiac arrest and could not be excluded without a new cranial computed tomography scan. In addition, due to the configuration of the brain stem intracranial hemorrhage, a systemic fibrinolytic therapy that would be the guideline-recommended treatment for cardiac arrest caused by a severe pulmonary embolism would highly likely have devastating consequences with inducing acute rebleeding of the intracranial hemorrhage and a high probability of a consecutive compression of the brain stem.

28.4 Treatment

In parallel to continuing advanced cardiac life support and multidisciplinary clinical workup and evaluation, code status and documentation of family conferences including potential advance care planning during the preceding ICU days was reviewed and an actual statement of the patient's surrogate decision-maker was obtained, indicating the patient's "Full Code-Status." With never ROSC within 45 min after start of CPR, an underlying disease with a relative contraindication for systemic fibrinolytic therapy and surgical embolectomy only available with a transfer of the patient to another center and besides this also requiring significant systemic anticoagulation for cardio-pulmonary bypass, multidisciplinary decision was made to start therapy with venous-arterial extracorporeal membrane oxygenation (VA-ECMO) as an ultimate therapeutic approach. During priming of the ECMO circuit, cannulation of femoral vein and artery, arrival of the ECMO team, and finally start of VA-ECMO therapy, high-quality advanced cardiac life support was continued. After approximately 120 min of CPR, extracorporeal circulation by a sufficiently running VA-ECMO system was accomplished and chest compressions could be stopped. A high blood flow was chosen for VA-ECMO therapy and initial systemic heparinization was omitted at this stage due to the unknown bleeding status of the brain stem intracranial hemorrhage. Following this, an urgent cranial computed tomography was obtained indicating neither a progress nor a rebleeding of the brain stem intracranial hemorrhage. Furthermore, massive bilateral central pulmonary embolism was confirmed with a computed tomography angiography of the thorax (Fig. 28.2). Therefore, in consensus with neurosurgery, therapeutic anticoagulation with continuous infusion of unfractionated heparin targeting a partial thromboplastin time of 60 s was started.

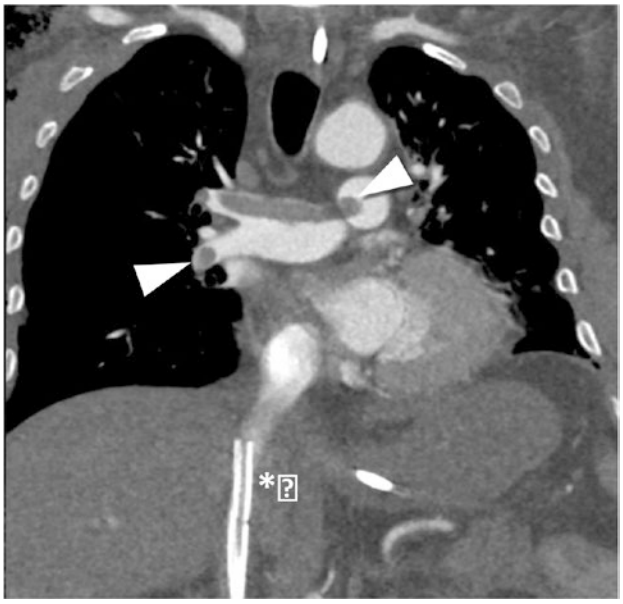

Fig. 28.2 Computed tomography angiography of the chest with a bilateral pulmonary embolism (white triangles) and ECMO cannula (*)

28.5 Evolution, Outcome, and Follow-Up

The thorax computed tomography also revealed dislocated rib serial fractures of the right hemithorax including a right-sided pneumothorax of 2 cm. The pneumothorax was relieved by insertion of a chest drain. In addition, post resuscitation, the patient developed a ventilator-associated pneumonia, which was treated with differentiated antimicrobial therapy. With a size constant organized brain stem intracranial hemorrhage in the follow-up cranial computed tomography scan 2 days later, therapeutic anticoagulation with continuous infusion of unfractionated heparin was further increased to target a partial thromboplastin time of 80 s. In the further course, a right-sided hematothorax developed which was treated with insertion of another chest drain and consecutive surgical evacuation of the organized hematoma 13 days after the cardiac arrest. With continuous dissolution of the pulmonary thrombi and hemodynamic stabilization, VA-ECMO therapy could successfully be weaned and the VA-ECMO circuit could be explanted after 14 days of treatment. Following this, complete weaning from sedation was possible and the patient showed an adequate wake up reaction. There was no new neurological deficit compared to the status before the cardiac arrest. Successful pulmonary weaning from mechanical ventilation was advanced and supported by intensive mobilization exercises under the guidance of the physiotherapists. With intensive swallowing exercises and dysphagia treatment by speech and language therapists, the patient began with an oral diet and was able to drink and eat solid food without signs for aspiration. With a fully controlled infection situation, fully

awake, and adequate and cardiopulmonary stable, the patient was discharged for final pulmonary weaning from the respirator, decannulation, and further neurological rehabilitation to a specialized neurorehabilitation clinic on ICU day 40 after the cardiac arrest. Although the patient did not attend follow-up with departments of our hospital, we received the information that after completion of neurorehabilitation, the patient was discharged home without a neurological deficit. His neurological function had recovered fully from the brain stem intracranial hemorrhage and the prolonged cardiac arrest.

28.6 Discussion

In cardiac arrest caused by acute pulmonary embolism, administration of a fibrinolytic therapy and continuous CPR for 60–90 min is recommended [1]. In a patient with a recent, 5-day-old brain stem intracranial hemorrhage, this might be a lethal approach. Likewise, surgical embolectomy requiring cardio-pulmonary bypass with significant systemic anticoagulation will result in an acute rebleeding episode or progression of the intracranial hemorrhage. Data on using VA-ECMO as a rescue therapy in cardiac arrest associated with pulmonary embolism are poor and mainly suggest VA-ECMO as a bridge to facilitate mechanical thrombectomy [2, 3]. However, in this case treatment with VA-ECMO allowed a bridging to radiographic imaging with exclusion of progression of the brain stem intracranial hemorrhage and a gold standard diagnosis of the massive pulmonary embolism as reason for the acute cardiac arrest. In addition, treatment with VA-ECMO allowed commencement of a patient-individualized anticoagulation management carefully balancing clot dissolution and rebleeding risk of the brain stem cavernoma.

Despite the advanced therapeutic approach using modern ICU organ replacement technology to treat the cause of the cardiac arrest, the favorable neurological outcome after almost 2 h of cardiac arrest was only achievable with an excellently performed guideline-compliant advanced cardiac life support. With the arrest occurring on the ICU under full noninvasive and invasive hemodynamic monitoring in a tracheostomized and sufficiently ventilated patient with advanced diagnostic tools such a blood gas analyzer and ultrasound device readily available at the bedside, advanced hemodynamic guidance and efficacy of CPR was executed from the beginning of the resuscitation efforts. Despite inconclusive and poor evidence to either support or refute extracorporeal CPR for both, out-of-hospital and in-hospital cardiac arrest, a minimal to zero no-flow time and adequate CPR including a short time window until the decision to commence VA-ECMO therapy are commonly agreed prerequisites for a potential favorable outcome of VA-ECMO therapy in treatment of cardiac arrest [4, 5]. Taken together, VA-ECMO might be a life-saving therapy in patients with an acute, massive pulmonary embolism and a recent, critical intracranial bleeding prohibiting other rescue therapies such as systemic fibrinolysis or mechanical thrombectomy.

Take-Home Messages

- Echocardiography in cardiac arrest situations might narrow the differential diagnosis of the reason for the cardiac arrest.
- VA-ECMO might be a life-saving therapy in patients with an acute, massive pulmonary embolism.
- VA-ECMO can be used as a bridge to decision as well as a bridge to recovery in cardiac arrest situations in which systemic fibrinolysis is contraindicated.
- Adequate and guideline compliant advanced cardiac life support under advanced hemodynamic monitoring and guidance with zero no-flow time can result in a favorable outcome even after hours of cardiac arrest.

Summary

A 50-year-old male admitted with a pontine intracranial hemorrhage suffered a sudden, witnessed cardiac arrest. Despite advanced cardio-pulmonary resuscitation (CPR), no return of spontaneous circulation was achieved and bedside echocardiography suggested a massive pulmonary embolism. While current guidelines recommend administration of a fibrinolytic therapy, this might be a lethal approach in a patient with a recent brain stem intracranial hemorrhage. Likewise, surgical embolectomy requiring cardio-pulmonary bypass with significant systemic anticoagulation was omitted. Data on using venous-arterial extracorporeal membrane oxygenation (VA-ECMO) as a rescue therapy in pulmonary embolism-cardiac arrest are poor and mainly suggest VA-ECMO as a bridge to facilitate mechanical thrombectomy. However, in this case treatment with VA-ECMO with high blood flow and without systemic heparinization allowed diagnosis of a central, bilateral pulmonary embolism with a computed tomography-angiogram followed by commencement of a patient-individualized anticoagulation management to balance pulmonary embolism-clot dissolution and rebleeding risk of the brain stem intracranial hemorrhage. Two weeks after the cardiac arrest, the VA-ECMO was removed and the patient recovered from the event without new neurological deficit. Therapy with VA-ECMO might be life-saving in patients with an acute, massive pulmonary embolism and a recent, critical intracranial hemorrhage prohibiting rescue therapies such as systemic fibrinolysis or mechanical thrombectomy.

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The Best Clinical Cases in Cardiovascular Medicine

Contents

Principles and Management of Rhythm Disturbances: Overview of Cardiac Arrest

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Contents

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Learning Objectives

- Understanding the different forms of rhythm disturbances
- Identifying life-threatening signs in tachyarrhythmia and bradyarrhythmia
- Implementing of ACLS algorithm in cardiac arrest
- Highlighting the importante of the chain of survival and post resuscitation care to improve neurological outcome after cardiac arrest

29.1 Introduction

The prevalence of critically ill patients admitted with cardiovascular-related diseases is increasing despite a decrease in the mortality related to this cohort of patients. Moreover, critically ill patients admitted with other organ dysfunctions can suffer from cardiovascular-related complications due to the unique nature of the cardiovascular system's synergy and overlap with another organ dysfunction. Therefore, the care of critically ill patients with cardiovascular problems is delicate because the threshold for decompensation is lower as their physiological reserve is easily compromised which leads to a mismatch in oxygen supply and demand as well as energy expenditure. Hence, cardiac output can be affected leading to impaired oxygen delivery to different organs and tissues resulting in potential tissue hypoxia, multi-organ dysfunction as well as failure.

Cardiovascular-related problems in critical care can be due to a primary cardiac cause such as acute myocardial infarction, arrhythmias and valvulopathies. Also, secondary non cardiac causes such as sepsis, acute pancreatitis, renal failure, ARDS and liver failure can be contributory to cardiac stress and even failure.

Critically unwell patients with cardiovascular-related diseases may present with a huge spectrum of clinical signs ranging from arrhythmias and hypotension to an overlapping complex picture of shock where more than one type could be present such as distributive vasoplegic and cardiogenic. Therefore, it is recommended to initiate multimodal haemodynamic monitoring tools which could include invasive blood pressure monitoring, advanced (invasive/non-invasive) haemodynamic monitors, central venous pressure tracing and echocardiography (both two-dimensional transthoracic echo cardiography and transoesophageal echocardiography according to the clinical scenario).

Management of these cohort patients is uniquely challenging because it is based on the analysis of variable haemodynamic parameters such as blood pressure, CVP, stroke volume, stroke volume variation, cardiac output, systemic vascular resistance and many other variables. Based on the interpretation of these variables, treatment modality can be delineated which could include a fluid bolus, vasopressors, inotropes or extracorporeal life support or indeed, a combination of them.

In this chapter, an introductory overview including case presentations on bradyarrhythmias, tachyarrhythmias and cardiac arrest will be presented and discussed.

29.1.1 Bradyarrhythmias

A bradyarrhythmia is a spectrum of abnormal cardiac rhythms, where the heart rate is below 60 beats/min. It could be normal in healthy athletic individuals as regular exercise increases the amount of oxygen taken to the heart as their heart muscles get stronger and pump a great volume of blood with each heartbeat. Also, it could be a sign of an underlying pathology such as myocardial infarction, sick sinus syndrome, hypothermia, hypokalaemia and drug toxicity (e.g. beta blockers and digoxin overdose). Identification of bradyarrhythmia aetiology and site is crucial as this determines the ongoing management [1].

29.1.2 Sinus Node Abnormalities

Sino-atrial node is the natural pacemaker of the heart, and it is responsible for heart conductivity, excitability and rhythmicity, and any abnormality in the sino-atrial node will impact the cardiac unique properties. There are various clinical presentations which involves sinus node dysfunction such as tachy-brady syndrome, chronic incompetence, sino-atrial exit block and inappropriate sinus bradycardia. The main common aetiology of sinus node abnormalities is idiopathic degenerative disease, and the spectrum of presentation varies from asymptomatic to syncope and presyncope [2].

29.1.3 Atrio-ventricular Conduction Abnormalities

Atrio-ventricular conduction blockades are classified into first, second and third degree. A first-degree AV block is a prolongation of the P-R interval more than 200 s, and it could be a normal variant in many subjects. Second-degree AV-block is subclassified in to Mobitz type 1 and Mobitz type 2. In Mobitz type 1 which is also called as Wenckebach phenomena, the PR interval prolongs until QRS complex drops which means that a normal P wave will not be followed by a regular QRS complex and its mainly nodal block. Whilst in Mobitz type 2, there is no PR prolongation and the QRS complex just drops, and it might be at fixed rate as 2:1 or 3:1 in coordination with the P wave. Its mainly infra-nodal where it could be anywhere below the AV node and hence the QRS complex is wider compared to Mobitz type 1 and is highly vulnerable to progress to complete heart block. Therefore, it is symptomatic and malignant. Third-degree heart block or complete heart block is a situation where no atrial activity (P wave) is conducted or transmitted through the atrio-ventricular node and the rest of the conduction system and as a result a junctional or ventricular escape rhythm will reflect the conductivity in the ventricles. Therefore, the ventricular rhythm will be regular but unrelated to the atrial rhythm and activity. In terms of ECG, P-R interval will be variable in timing whilst R-R interval will be regular. In summary, atrial and ventricular activity will be dissociated [3].

29.1.4 Junctional Abnormalities

These are abnormalities which originate from the area around the atrio-ventricular node which could involve the AV node, supra bundle heart fibres and the bundle of His. If the block is at this level, the intrinsic rate is around 30–60 beats/min which replaces the ventricular idiopathic rhythm which has an intrinsic rate of 0–40 beats/min. As a result, a faster ventricular rate results when compared to complete heart block.

29.1.5 Intraventricular Conduction Abnormalities

These are a group of conduction disturbances which occurs below the AV node, and they are categorized based on the anatomical location of defects in the conductive system. In terms of clinical presentation, *intraventricular conduction abnormalities* do not cause bradycardia but might lead to bradyarrhythmia if they are associated with other clinical scenarios such as acute myocardial infarction,

Classes of Intraventricular Conduction Abnormalities

- Uni-fascicular block resembles the affection of one fascicle and could be either right bundle branch block (RBBB), left anterior fascicular block (LAFB) and left posterior fascicular block (LPFB).
- Bi-fascicular block which represents conduction abnormalities in two fascicles, such as left bundle branch block (LBBB) or RBBB with either (LAFB) or (LPFB).
- Tri-fascicular block represents conduction abnormalities in three fascicles or when there is a combination of bi-fascicular blockade.

29.1.6 Management

In any patient with bradyarrhythmia, the first fundamental step in assessment is the ABCDE approach because it will allow the physician to assess the clinical status of the patient as well as intervene accordingly and in the meantime determine the provisional contributing factor. The first step is to provide oxygen, and target oxygen saturations will be tailored according to different patient cohorts such as acute myocardial patients; target saturations will be 94–98%. Then, IV access should be obtained and sent for laboratory investigation according to the clinical scenario such as urea and electrolytes. The next step is to establish monitoring such as ECG telemetry, non-invasive blood pressure and 12 lead ECG. As a result, reversible causes should be identified and treated such as electrolyte disturbance [4].

The next parallel cornerstone step in the bradyarrhythmia algorithm is to assess for evidence of life-threatening signs which are shock, syncope, myocardial ischaemia and heart failure. If there is not any of the life-threatening signs, risk of asystole should be assessed and if there is no risk of asystole the patient should only be observed [1].

On the other hand, if the patient has any of the life-threatening signs, the initial treatment should be atropine 500 mcg IV; if there is a satisfactory response, the patient should be assessed for risks of asystole; and if none of them is present, the

patient should be only observed. But if the patient didn't have a satisfactory response for atropine, interim measures should be started. Atropine 500 mcg IV could be repeated every 3–5 min to maximum of 3 mg, and if there is no effect with the vagolytic action of atropine, chronotropic drugs such as isoprenaline 5 mcg/min IV or adrenaline 2–10 mcg/min IV can be used.

Also, alternative drugs can be used as interim measures to increase the heart rate through various mechanisms of action. For example, aminophylline 100–200 mg via slow intravenous infusion (especially in patients who had inferior myocardial ischaemia, heart transplant and spinal cord injury). In cases of beta blocker and calcium channel blocker toxicity, consider glucagon which can act as a chronotrope and inotrope through different receptors. In cases of heart transplant, glycopyrrolate can be used instead of atropine because atropine could lead to high AV block or sinus arrest aminophylline could be used instead. At this stage, if there is no response to any of the interim drug therapies, pacing should be considered especially in patients who are haemodynamically unstable, and if transthoracic pacing is unsuccessful, expert help should be sought to consider and arrange for transvenous pacing.

In systolic patients, ECG should be checked for P wave presence because it might not be true asystole and responds to cardiac pacing [3].

If patients were assessed for risks of asystole which involves recent asystole, Mobitz type 2 AV block, complete heart block with wide QRS complex and ventricular standstill for 3 s and had one of these risk factors, interim measures mentioned before should be started, and if there were no response, experts' review and opinion is mandatory to consider and arrange for transvenous pacing [2].

In the meantime, transcutaneous pacing can be initiated which could be painful. Therefore, it is recommended to use sedation and analgesia to avoid pain associated with transcutaneous pacing. If transcutaneous pacing is not immediately available in the 2021 UK resuscitation council guideline, but not the ERC guideline, percussion pacing could be initiated which is serial of rhythmic blows with closed fist over the lower edge of the sternum to restart the physiological pacemaker SAN at a rate of 50–70 beats/min [1].

29.2 Tachyarrhythmias

A tachyarrhythmia is an abnormal cardiac rhythm, with a heart rate greater than 100 beats/min. Identification of the type of tachyarrhythmia is important as this determines the ongoing management.

The first step is identifying whether any life-threatening features are present. These are more commonly seen with a heart rate greater than 150 beats/min. At this rate, the time in diastole is shortened, there is insufficient time for cardiac filling, cardiac output is reduced, and there is decreased coronary blood flow with resultant myocardial ischaemia. In patients with a pre-existing cardiac history or other significant medical co-morbidities, this can occur at a lower heart rate. Adverse features include the presence of any one of shock, syncope, myocardial ischaemia or severe cardiac failure. When one or more of these are present with a tachyarrhythmia, synchronized DC cardioversion should be attempted. Appropriate sedation should be given and up to three synchronized shocks delivered. Delivery of a synchronized

shock means that the shock is delivered to coincide with ventricular depolarization, the R wave on the ECG. A synchronized shock is used to prevent potentially precipitating ventricular fibrillation, if, for example, the shock coincides with ventricular repolarization, the T wave. If electrical cardioversion is unsuccessful, then administration of 300 mg intravenous amiodarone should be considered [5].

Tachyarrhythmias can be divided into broad or narrow complex rhythms. If the QRS depth is less than 0.12 s, they are narrow complex and those more than 0.12 s broad complex.

29.2.1 Broad Complex Tachycardias

These are either a ventricular rhythm or a supraventricular rhythm where conduction has been altered due to a bundle branch block.

29.2.2 Ventricular Tachycardia (VT)

VT is defined as more than three ventricular ectopic beats, at a rate of at least 130 beats/min. If it continues for more than 30 s, it is considered to be sustained VT. The principles covered in this section will refer to VT that is associated with a cardiac output. Pulseless VT will be reviewed in the section on cardiac arrest. VT with a pulse is always at risk of deteriorating to cardiac arrest. The most common type of VT is monomorphic VT, caused by myocardial ischaemia. It is managed with a loading dose of intravenous amiodarone, 300 mg given over 20 min. If this is successfully in reverting the VT, a 24-h infusion of 900 mg of amiodarone should be given to complete the intravenous loading dose. If VT persists after the 300 mg of amiodarone, then synchronized cardioversion may be indicated, with appropriate sedation. Other drug therapies that can be considered include sotalol, procainamide or verapamil. The underlying cause must also be treated, for example, by cardiac revascularization if myocardial ischaemia was the precipitant.

Following initial management of VT, patients will need to be reviewed for consideration of an implantable cardioverter defibrillator (ICD) if recurrence of the arrhythmia is considered likely [6].

29.2.3 Polymorphic VT

This is a particular subgroup of VT and includes torsades de pointes. Its classical ECG appearance is produced by a changing axis of electrical activity. It is most commonly seen in patients with a prolonged QT interval, either secondary to drugs or familial causes. Patients are commonly either hypokalaemic or hypomagnesaemic. Drugs that prolong the QT, including amiodarone, are contraindicated in the management of torsades de pointes. The mainstay of treatment is removal of precipitating causes, correction of any electrolyte derangements, and intravenous magnesium, 2 g given over 20 min, even in the absence of hypomagnesaemia. Once reverted, overdrive pacing may be required to prevent recurrence [6].

29.2.4 Supraventricular Rhythms with Bundle Branch Block

These should be managed in the same way as arrhythmia that presents, without bundle branch block. This will be covered later in this section. However, a rare but important differential that should be excluded is AF in a patient with Wolff-Parkinson-White syndrome (WPW). This is a form of atrio-ventricular re-entry tachycardia where ventricular pre-excitation occurs with the arrhythmia transmitted via an accessory pathway. This risks converting to ventricular fibrillation as the AV node normally limits transmission between the atrium and ventricles, but in the presence of an accessory pathway, the rapid atrial activity can be transmitted unopposed to the ventricles. Management requires use of antiarrhythmics that will prolong transmission through the accessory pathway; this includes sotalol or amiodarone [7].

29.2.5 Narrow Complex Tachycardias

Sinus tachycardia is not an arrhythmia, but a physiological response and treatment should focus on the underlying cause.

29.2.6 SVT

SVT refers to a tachycardia arising above the bundle of His and includes a number of different rhythms. However, it is commonly used to describe atrio-ventricular nodal re-entry tachycardias (AVNRTs), a regular narrow complex tachycardia. Vagal manoeuvres should be trialled to revert a regular narrow complex tachycardia; these may include carotid sinus massage or a Valsalva manoeuvre. They are successful in reverting the rhythm 25% of the time. If they are unsuccessful and there is no pre-excitation on an ECG, then adenosine should be given as a rapid injection via large bore venous access. An initial dose of 6 mg, escalating to 12 mg then 18 mg if the SVT does not revert. Patients should be warned of the side effects prior to administration of adenosine, including chest discomfort and a feeling of breathlessness, lasting several seconds. If adenosine does not revert the SVT, it may transiently slow to enable identification of the underlying rhythm. Beta blockers, verapamil or diltiazem may be used for rate control if adenosine is unsuccessful. Synchronized DC cardioversion can be considered, with adequate sedation, if none of the above methods are successful or the patient is unstable secondary to the tachyarrhythmia [7].

29.2.7 Atrial Flutter

Atrial flutter is the second most common pathological SVT. The management has some similarities to that of atrial fibrillation. However, drugs that block the AV node should be avoided. Therefore, where atrial flutter is known to be the underlying rhythm, adenosine should not be given and beta blockers form the mainstay of treatment for rhythm control.

29.2.8 AF with Rapid Ventricular Response

This is an irregular narrow complex tachycardia. As with all tachyarrhythmias in the presence of any of the four life-threatening features, synchronized cardioversion should be performed. If no life-threatening features are present, then management will vary based on whether the AF is a new or chronic condition. If new and the onset time is known and within 48 h, then it is important to try to convert to their usual rhythm; this is either with electrical or chemical cardioversion. Chemical cardioversion is less likely to be successful but is also less invasive and is usually performed using intravenous amiodarone. If the AF has been present for longer than 48 h, a transoesophageal echo should be performed to exclude an atrial thrombus, or the patient must be fully anticoagulated for at least 3 weeks prior to cardioversion [5].

Prior to cardioversion or if the AF is chronic and rate control is required, then the cause for deterioration should be assessed and treated where possible. Electrolytes should be replaced, particularly potassium and magnesium. For rhythm control, beta blockade is usually first line, unless a contraindication exists. Diltiazem or verapamil may be used as an alternative. Digoxin has a slower onset time and is a second-line treatment for rate control in AF [8].

29.3 Cardiac Arrest

Sudden cardiac arrest is the abrupt loss of heart function, breathing and consciousness. The annual incidence of out–of-hospital cardiac arrest (OHCA) in Europe is between 67 and 170 per 100,000 inhabitants and for in-hospital cardiac arrest (IHCA) ranges between 1.5 and 2.8 per 1000 hospital admissions.

Outcomes from cardiac arrest are usually poor, with survival ranging from 8 to 10% for OHCA and from 15 to 34% for IHCA, depending on the registries [9]. Sequelae among survivors can range from neurocognitive, fatigue and emotional problems that lead to a reduced quality of life to persistent vegetative state in the most severe cases.

Survival and neurological outcome are time-sensitive and depend on the social and health system performance from the first seconds after the arrest, including bystander cardiopulmonary resuscitation (CPR), early defibrillation, early advanced life support and standardized post-resuscitation care. These interventions are known as the chain of survival [10].

29.3.1 Causes and Physiopathology of Cardiac Arrest

Cardiac arrest is a consequence of cardiocirculatory dysfunction caused by pump or circulatory failure. Causes of pump failure can be electrical (arrhythmias of any cause leading to impaired pump function) or mechanical (myocardial dysfunction or valvular failure). Circulatory collapse may be the result of obstructive, hypovolaemic, or distributive shock. Cardiocirculatory collapse leads to generalized hypoperfusion and organ failure.

Table 29.1 Causes of cardiac arrest. Reversible causes are often referred as 4 Hs and 4 T, being hypoxia, hypovolaemia, hyper-/hypokalaemia, hypothermia, tension pneumothorax, tamponade, toxins and thrombus

Pump failure	Circulatory failure
• Ischaemia • Arrhythmias – Primary – Secondary (ischaemic, electrolytic imbalances, hypothermia, toxic, pharmacological, adrenergic storm, etc.). • Cardiomyopathy • Valvular disease • Congenital heart disease • Hypoxaemia	• Hypovolaemic shock – Aortic syndrome – Trauma – Burns – Gastrointestinal disease • Distributive shock – Anaphylaxis – Sepsis • Obstruction (pulmonary embolism, cardiac tamponade, pneumothorax)

Eighty percent of cases of sudden cardiac arrest are caused by primary cardiac disease (Table 29.1).

From a physiological point of view, a time-dependent three phase model [11] has been proposed for cardiac arrest caused by arrhythmias:

- Electrical phase: from the onset of cardiac arrest to approximately 4 min after the arrest. During this phase, the heart still has some residual oxygen supply and can respond well to defibrillation.
- Circulatory phase: from 4 to 10 min after cardiac arrest. During this phase, hypoperfusion can perpetuate heart arrhythmia. CPR provides oxygen delivery and increases the chances of a successful defibrillation.
- Metabolic phase: beyond 10 min after cardiac arrest. Tissue ischaemia sets in, and chances of successful defibrillation decrease over time. CPR may be able to provide sufficient perfusion preserve brain function until the cause of cardiac arrest is treated or other interventions such as extracorporeal cardiopulmonary resuscitation (ECPR) are initiated.

29.3.2 Cardiopulmonary Resuscitation

Cardiopulmonary resuscitation is a technique that consists of a series of measures to guarantee enough blood circulation and oxygen delivery to preserve organ function until the recovery of spontaneous circulation.

Detection of cardiac arrest is the first step to implement these measures. A basic primary survey that addresses level of consciousness, airway patency and breathing should be performed. If the patient is unconscious, and not breathing (or presents agonic breathing) through a patent airway, cardiac arrest is diagnosed. After diagnosis, the priority is to call for support and start basic life support measures.

29.3.2.1 Basic Life Support

High-quality chest compressions are key to maintain organ perfusion, as they can generate a cardiac output of 24–40% of the pre-arrest values.

Circulation stops when the pressure difference between the right atrium and the aorta equalizes, which happens during the first minutes of cardiac arrest. Chest compressions maintain blood flow through two mechanisms: cardiac pump and thoracic pump. Compression of the chest empties the heart and the thoracic vessels, sending blood toward the periphery and filling again during decompression. Uninterrupted, repeated chest compressions can generate an accumulated pressure gradient of 60–80 mmHg that quickly dissipates after their interruption.

High-quality chest compressions are performed at a rhythm of 100–120 compressions per minute, at a depth of 5–6 cm, allowing thorax decompression. They should be performed over a firm surface and with the rescuer's hands placed in the lower third of the sternum. Suboptimal compression technique is directly related to mortality [12].

Ventilations should be performed, if possible, with a ratio of 30 chest compressions to two ventilations.

Early defibrillation with an automated external defibrillation is safe, can be performed by laypeople and increases the chances of recovering from the cardiac arrest.

29.3.2.2 Advanced Life Support

Advanced life support includes all the advanced interventions after basic life support and is directed to treating the reversible causes of cardiac arrest.

Compared to basic life support, advanced life support includes identifying periarrest conditions and patients at risk for cardiac arrest, airway management, optimized defibrillation, vascular access, drugs and fluids [13]. An overview is presented in ◘ Fig. 29.1; for details see the appropriate guidelines (e.g. European Resuscitation Council Guidelines).

29.3.3 Post-resuscitation Care

Post-resuscitation care covers all the interventions directed to stabilize, treat reversible causes and prognosticate after CRP.

- Diagnosis: if there is a presumed cardiac cause, coronary angiography should be prioritized. Computed tomography (CT) scan (chest and brain) should follow if the coronary angiography fails to demonstrate any cause.
- Airway and ventilation: patients who remain comatose after resuscitation have an indication for sedation and mechanical ventilation and should be intubated. Oxygenation and ventilation should target usual values (saturation of 94–98%, pCO_2 35–45 mmHg).
- Circulation: post cardiac arrest shock may be cardiogenic or distributive. The targets should be avoiding hypotension and maintaining perfusion with fluids, vasoactive and inotropic drugs. Mechanical circulatory support can be considered if the patient fails to recover from cardiogenic shock.
- Neurological recovery: seizures are frequent and should be diagnosed. Antiepileptic drugs can be used but do not modify prognosis. Targeted temperature management (TTM) can be considered. Fever should be avoided for at least 72 h after ROSC.

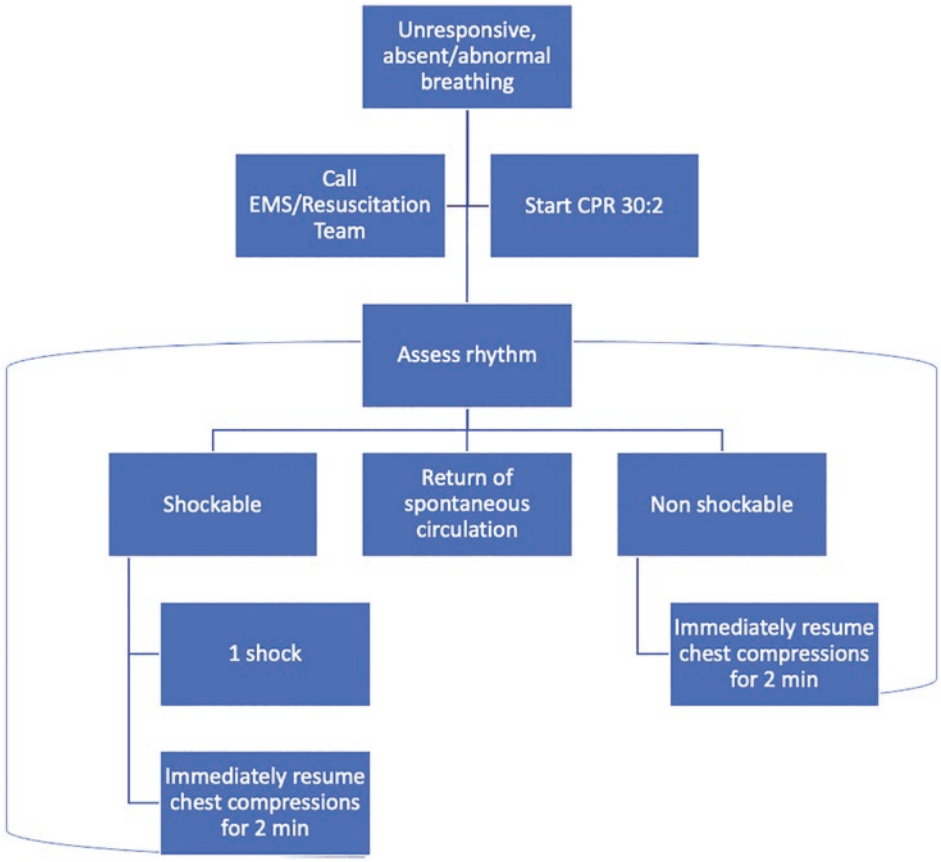

Fig. 29.1 Advanced life support algorithm. *CPR* cardiopulmonary resuscitation; *EMS* emergency medical system; *PEA* pulseless electrical activity; *ROSC* return of spontaneous circulation; *VF* ventricular fibrillation; *VT* ventricular tachycardia. Modified from the European Resuscitation Council Guidelines 2021: adult advanced life support

- Prognostication: a multimodal prognostication strategy using CT scan, electroencephalography, neurophysiology (somatosensory-evoked potentials), biomarkers and clinical examination should be performed [14].

Take-Home Messages

- Survival and neurological outcomes after cardiac arrest are time-sensitive.
- Early basic life support with high-quality chest compressions and early defibrillation are the key interventions that affect prognosis.
- Extracorporeal cardiopulmonary resuscitation can be considered in refractory cases.
- Post resuscitation care is directed to stabilize, diagnose and treat reversible causes and establishing prognosis after cardiac arrest.

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Arrhythmias: Electrical Storm in a COVID-19 Patient

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Contents

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Learning Objectives

- Arrhythmias could manifest in the context of COVID-19.
- Differential diagnosis of electrical storm is broad and complicated.
- Electrical storm treatment is urgent and multidisciplinary.

30.1 Introduction

Apart from respiratory failure and acute respiratory distress syndrome, COVID-19 infection has been associated with multiple organ injuries and complications. Cardiac complications due to COVID-19 are commonly described in the literature and include myocarditis, myocardial injury, heart failure, and arrhythmias. The latter often include supraventricular and atrial arrhythmias but rarely ventricular arrhythmias [1]. Direct viral injury and systemic inflammation have been hypothesized to trigger cardiac complications. However, the arrhythmogenic role of SARS-CoV-2 remains unclear.

Electrical storm refers to a state of cardiac electrical instability that is defined by three or more episodes of sustained ventricular tachycardia or ventricular fibrillation or three or more appropriate shocks from an implantable cardioverter defibrillator within 24 hours [2]. It is a life-threatening condition that requires urgent treatment, including sympathetic blockade with sedation and intubation, beta blockers and antiarrhythmic drugs, and intervention techniques, such as catheter ablation. Recurrences are common and can be catastrophic.

To our knowledge, there is scarce evidence directly linking SARS-CoV-2 infection and ventricular arrhythmias. Very few cases of electrical storm in COVID-19 patients have been reported in the literature [1–6]. In this presentation, we aim to describe a case of electrical storm in a COVID-19 patient who, following cardiac arrest, was admitted to the intensive care unit.

Case Presentation

A 56-year-old woman was admitted to the cardiology department presenting the following symptoms: shortness of breath, edema of bilateral lower extremities, and palpitations. She reported that these symptoms started 4 days prior to admission. Her medical history included hypertension and a benign thyroid nodule. She reported no prior medical history of left ventricular dysfunction or coronary artery disease. She had not been vaccinated against COVID-19. She presented hemodynamically stable, afebrile, but sweaty with difficulty breathing. Auscultation revealed bilateral coarse crackles. Oxygen saturation was 89% on air.

30.2 Investigations

Initial electrocardiography revealed an irregular rhythm with narrow QRS intervals and absence of P waves suggesting a previously unknown atrial fibrillation along with a rapid ventricular response of 170 beats per minute and a QTc interval equal to 488 ms. During echocardiography, global hypokinesia of the left ventricle was found, along with a left ventricular ejection fraction of 30–35%. Cardiac markers were negative for myocardial injury. A computed tomography pulmonary angiogram excluded pulmonary embolism and showed no lung infiltrates. Following a transesophageal echocardiogram that ruled out the presence of atrial thrombi, synchronized cardioversion was performed successfully. Subsequently, the patient presented recurrent episodes of non-sustained ventricular tachycardia and one episode of unstable polymorphic ventricular tachycardia which was treated with defibrillation and, afterward, administration of amiodarone.

As she developed a low-grade fever, a nasopharyngeal swab was obtained to test for SARS-CoV-2 by polymerase chain reaction. Due to a positive result, she was transferred to the COVID-19 department where she suffered a cardiac arrest. After an advanced life support rotation with a total duration of 10 min, she was resuscitated and transferred to the intensive care unit where she presented multiple recurrent episodes of sustained polymorphic ventricular tachycardia (electrical storm) along with episodes of non-sustained polymorphic ventricular tachycardia (Fig. 30.1). After conversion to sinus rhythm, QT prolongation (QTc = 568 ms) was detected, indicating torsade de pointes.

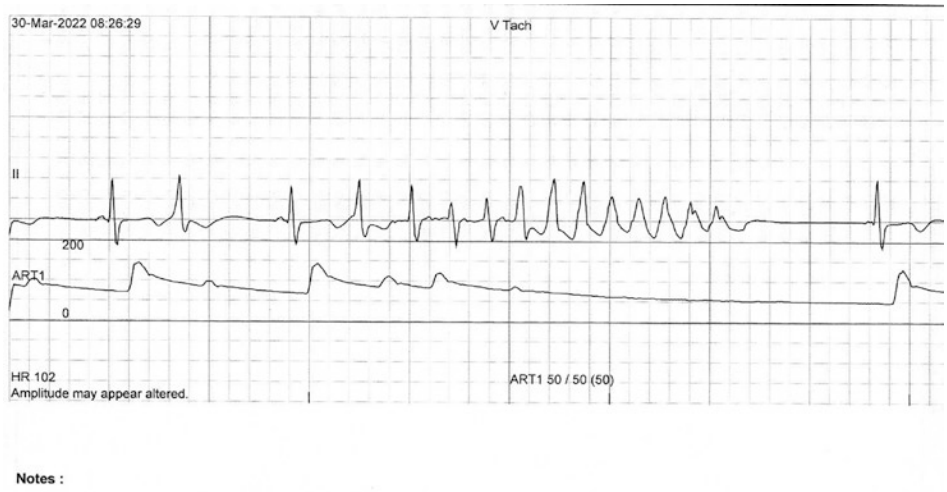

Fig. 30.1 Polymorphic ventricular tachycardia in a COVID-19 patient

30.3 Differential Diagnosis

Electrical storm can be triggered by acute myocardial ischemia, electrolyte imbalances such as hypokalemia, decompensated heart failure, hyperthyroidism, infection, fever, channelopathies such as Brugada syndrome, and long QT syndrome and QT prolonging medications [6]. Interestingly, a trigger for electrical storm is not identified in over 80% of the cases.

In the presented case, laboratory results excluded acute myocardial ischemia and electrolyte imbalances. Amiodarone was discontinued due to QT prolongation. Left ventricular ejection fraction was found to be 15% at the time of admission to the intensive care unit, and B-type natriuretic peptide was 827 pg/ml (normal values <100 pg/mL). Thyroid hormone panel was normal. Inflammation markers were elevated; interleukin six levels were 51 pg/mL (normal values <17 pg/mL); as well as C-reactive protein levels were 7.4 mg/dL (normal values <0.8 mg/dL), but except for SARS-CoV-2, no other infectious agent was detected.

30.4 Treatment

Intravenous magnesium was administered along with continuous infusion of landiolol and loop diuretics. A temporary transvenous pacer was placed and overdrive pacing was initiated. Gradually, the recurrence intervals grew wider and the incidences of ventricular tachycardia completely subsided after 48 h. The patient remained on mechanical ventilation with FiO2 equal to 45% and positive end-expiratory pressure of 6 cmH_2O on volume control ventilation with tidal volume equal to 420 mL, presenting relatively good lung compliance and respiratory mechanics. During echocardiography reassessment on day 15 in the intensive care unit, left ventricular ejection fraction was found to be 45% and left ventricle wall motion was improved.

30.5 Evolution, Outcome, and Follow-Up

The patient subsequently stabilized and was eventually weaned off the ventilator. She managed to breathe spontaneously through a tracheostomy tube. She exhibited no respiratory failure with no need for diuretics or heart rate control medication. However, she suffered grave neurological injury secondary to cardiac arrest. Magnetic resonance imaging of the brain revealed signs of bilateral cortical laminar necrosis, due to generalized cerebral hypoperfusion. During a 3-month follow-up period, she remained stable, with no recurrence of ventricular arrhythmias. Per her family request, she did not undergo further investigation with cardiac magnetic resonance imaging.

30.6 Discussion

Most electrical storm cases present with sustained monomorphic ventricular tachycardia, which often occurs in the context of a severe structural heart disease. Rarely, electrical storm presents with polymorphic ventricular tachycardia,

Table 30.1 Previous case reports of electrical storm in COVID-19 patients

First author	Year	Patient age	ICD	Arrhythmia	Long QT	Brugada syndrome	QT prolonging drugs
Doodnauth [1]	2021	95	No	VT	No	No	No
Vetta [2]	2020	78	Yes	VT	Yes	No	Hydroxychloroquine
O'Brien [3]	2020	82	No	Polymorphic VT	Yes	No	Amiodarone, trazodone
Maglione [4]	2020	58	Yes	VF	Yes	Yes	Hydroxychloroquine
Elssaid [5]	2020	55	No	VF	Yes	No	No
Mitacchione [6]	2020	68	Yes	VT	No	No	No

ICD implantable cardioverter defibrillator; *VF* ventricular fibrillation; *VT* ventricular tachycardia

as in the case presented. Polymorphic ventricular tachycardia is usually associated with myocarditis and hypertrophic cardiomyopathy while it is of crucial importance to investigate for QT prolongation as soon as sinus rhythm is recovered.

Six other cases have been reported associating ventricular arrhythmia storm with COVID-19 (Table 30.1). Three of them accounted for electrical storm patients presenting monomorphic ventricular tachycardia, two for patients with ventricular fibrillation and only one for a patient with polymorphic ventricular tachycardia. QT prolongation was detected in four cases, three of which could be associated with QT prolonging medications. In our case, the first episode of polymorphic ventricular tachycardia occurred before amiodarone administration. Based on clinical findings, we assume that decompensated heart failure could have been a trigger for ventricular arrhythmias along with COVID-19 infection. Cardiac function was notably impaired at presentation, but it improved after COVID-19 resolution.

The underlying causal mechanism of cardiac arrhythmias in COVID-19 patients is not clear. Cytokine storm, elevation of intracellular calcium due to hypoxia, and myocardial injury are some elements that could increase the likelihood of arrhythmogenesis in COVID-19.

COVID-19 patients in the intensive care unit predominantly present respiratory complications, severe pneumonia, and ARDS, and they often manifest cardiac complications proportional to their COVID-19 severity. This case presentation highlights arrhythmogenesis in COVID-19 as a serious cardiac complication, with potentially fatal outcomes, even in patients who present relatively mild lung involvement.

Take-Home Messages

- Prompt diagnosis of electrical storm and other arrhythmias is crucial in COVID-19 patients.
- In polymorphic ventricular tachycardia, always look for QTc prolongation as soon as sinus rhythm is recovered.
- Ventricular arrhythmias can occur even in COVID-19 patients with mild respiratory complications.

Summary

Apart from the respiratory tract, COVID-19 infection has proven to affect multiple organs, especially the cardiovascular system. Cases of myocarditis, myocardial injury, heart failure, and arrhythmias have been documented in COVID-19 patients. Ventricular arrhythmias and electrical storm, a state of recurrent ventricular arrhythmias, can be a rare complication. We describe the case of a 56-year-old woman who manifested electrical storm as a COVID-19 patient. She was admitted to the cardiology department due to shortness of breath, edema of bilateral lower extremities, and palpitations. She was subjected to synchronized cardioversion for atrial fibrillation. Afterward, she presented episodes of non-sustained ventricular tachycardia and one episode of unstable polymorphic ventricular tachycardia which was treated with defibrillation and amiodarone. During investigations for a low-grade fever she presented, she was tested positive for SARS-CoV-2. After her transfer to the COVID-19 department, she suffered a cardiac arrest and underwent advanced life support resuscitation. Following resuscitation, she was transferred to the intensive care unit where she presented electrical storm of polymorphic ventricular tachycardia in the context of QT prolongation. Acute myocardial ischemia, electrolyte imbalances, and thyroid dysfunction were excluded. Intravenous magnesium was administered and a temporary transvenous pacer was placed for overdrive pacing. She presented no serious respiratory complications from COVID-19. The patient gradually stabilized and was weaned off the ventilator breathing spontaneously through a tracheostomy tube. She was diagnosed with bilateral cortical laminar necrosis secondary to cardiac arrest. During a 3-month follow-up, she remained stable, with no recurrence of ventricular arrhythmias. Six other cases of electrical storm in COVID-19 have been reported, half of which documented recurrent monomorphic ventricular tachycardias. Electrical storm rarely manifests with polymorphic ventricular tachycardia, as in the case presented. Arrhythmogenesis in COVID-19 is a serious cardiac complication which can be life-threatening even in patients with mild lung involvement.

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A Case of Near-Fatal Chronic Digoxin Toxicity

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Contents

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Learning Objectives

- A review of the pharmacology of cardiac glycosides
- The presentation and management of life-threatening complications of chronic digoxin therapy
- The pitfalls and challenges of managing a critically ill patient with digoxin toxicity

31.1 Introduction

Cardiac glycosides are a family of naturally occurring cardioactive steroids, found widely in plant and animal species. They remain an important cause of poisoning worldwide, most commonly reflecting their ongoing clinical use as a treatment for atrial fibrillation and congestive cardiac failure, though sporadic poisoning from *Nerium* (oleander) and *Digitalis* (foxglove) plants continues to occur annually.

The primary mechanism of cardiac glycosides is through inhibition of sodium-potassium adenosine triphosphatase (Na+/K+ -ATPase) enzymes. This is a ubiquitous and essential transmembrane enzyme that stabilises the resting membrane potential of cells and supports electrochemical ion gradients required for osmotic equilibrium within cells and cell-signal transduction between cells. A secondary effect of cardiac glycosides is through an augmented vagal output from the nucleus tractus solitarius, resulting in parasympathomimetic effects upon cardiac muscarinic receptors within the atria and atrioventricular node.

The resultant effects of cardiac glycosides upon the myocardium are a combination of positive inotropy, negative chronotropy, and negative dromotropy which make them attractive agents for use in managing atrial tachydysrhythmias and congestive cardiac failure. However, their clinical usage has declined in recent years, as pharmacological agents with improved efficacy and better side effect profiles have been integrated into clinical practice. Moreover, recent data demonstrates an increase in all-cause mortality amongst patients with atrial fibrillation treated with digoxin [1].

Cardiac glycoside toxicity is broadly presenting and ranges from abrupt life-threatening cardiac dysrhythmias, through to insidious presentations of non-specific illness and gastrointestinal upset. As a result of its long half-life and predominant renal excretion, plasma digoxin concentrations can rise to toxic levels in the context of acute kidney injury. Amongst the elderly population, vague symptoms are typical and include dizziness, fatigue, visual changes, and dyspnoea. Whilst relatively uncommon, it is important to directly enquire about xanthopsia (a yellow-green visual discolouration)—a classic, but non-pathognomonic, finding in cardiac glycoside toxicity.

Despite the narrow therapeutic index and potentially fatal adverse effects, digoxin remains staunchly embedded in clinical use, and thus a detailed understanding of the breadth of presentations of cardiac glycoside toxicity and its effective management remain essential for the critical care physician.

Case Presentation

An 83-year-old male self-presented to the gastroenterology day unit for an elective abdominal paracentesis. His clinical history was notable for Child-Pugh B cirrhotic liver disease associated with ascites refractory to diuretics, for which he underwent 4-weekly abdominal paracenteses. Other relevant background included a recent spironolactone-induced acute kidney injury, atrial fibrillation, non-insulin-dependent diabetes mellitus, and gout. His routine medications were digoxin 250 micrograms once daily, carvedilol 6.25 mg twice daily, apixaban 5 mg twice daily, metformin 500 mg twice daily, spironolactone 150 mg once a day (recently reintroduced), and simvastatin 10 mg once daily.

Despite his co-morbidities, he retained complete functional independence, continued to drive, had an unlimited exercise tolerance, and had recently retired from his work to act as the full-time carer for his wife who suffered with vascular dementia.

On admission to the day unit, the patient was said to feel well. His admission blood pressure was 126/82, pulse rate of 83, and a respiratory rate of 16 breaths/min with a SpO2 of 100% on room air. Clinical examination revealed a well, elderly male with no physiological compromise. His abdomen was tense and distended. Abdominal ultrasound confirmed large-volume ascites with a minimum depth of 5 cm noted in the right iliac fossa. It was confirmed that his apixaban had been held for 48 h prior to admission. Insertion of a right iliac fossa ascitic drain continued uneventfully and an initial 2 L of ascites drained. At this point the drain was clamped and, in accordance with the day unit's protocol, 100 mL of 20% human albumin solution administered intravenously, prior to further ascitic drainage.

At this time, the patient complained of dizziness and collapsed with loss of consciousness. He was found to be pulseless and external cardiac massage commenced by the ward nursing team. An automatic external defibrillator was applied and a non-shockable rhythm confirmed. Signs of life returned after 45 s of cardiopulmonary resuscitation, and verbal contact was thereafter maintained with the patient until arrival of the medical emergency team.

31.2 Resuscitative Management

On arrival of the medical emergency team, the patient was maintaining his own airway, spontaneously ventilating at a rate of 14 breaths/min. Oxygen was applied at 15 L/min via a non-rebreathe mask. No SpO2 trace was obtainable, which was felt to be secondary to poor peripheral perfusion. A strong carotid pulse was present at a

rate of approximately 10 beats/min, and a 3-lead electrocardiogram confirmed complete heart block with an electrical rate of 12/min. A non-invasive blood pressure was unrecordable, but verbal contact was maintained with the patient who had a Glasgow Coma Score of 15/15.

Given his precarious haemodynamic status, an immediate trial of 1 mg of intravenous atropine was attempted with no response. Boluses of intravenous adrenaline were administered in 100 μg aliquots totalling approximately 500 μg with minimal transient effect. Transcutaneous pacing was attempted with pads placed in the anterolateral configuration, but there was failure to capture at the maximal current of 140 mA. At this point, the patient demonstrated declining cerebration and impending cardiopulmonary arrest was recognised. A further attempt at transcutaneous pacing was made with fresh pads place in an anteroposterior configuration and electrical and mechanical capture obtained at 80 mA. Thereafter, the patient was paced at a rate of 90/min at 140 mA with return of haemodynamic stability, improving consciousness level, complaining of significant pain secondary to transcutaneous pacing. The cardiology service was urgently contacted, and a decision made to proceed to emergent implantation of a single-chamber permanent pacemaker.

To facilitate safe transfer to the cardiac catheterisation laboratory, the patient underwent rapid sequence induction of anaesthesia with midazolam and rocuronium, was endotracheally intubated, and sedated with a propofol infusion. A left radial arterial line was inserted for invasive blood pressure monitoring, and the patient was urethrally catheterized for urine output monitoring.

On arrival in the cardiac catheterisation laboratory, it was confirmed that the patient's underlying cardiac rhythm was now P-wave asystole with ventricular standstill. A single-lead VVI Medtronic® permanent pacemaker was uneventfully inserted via the left axillary vein, and the patient was transferred to the critical care unit for ongoing care. His post-procedure ECG showed a paced rhythm at 90 beats/min (Fig. 31.1a).

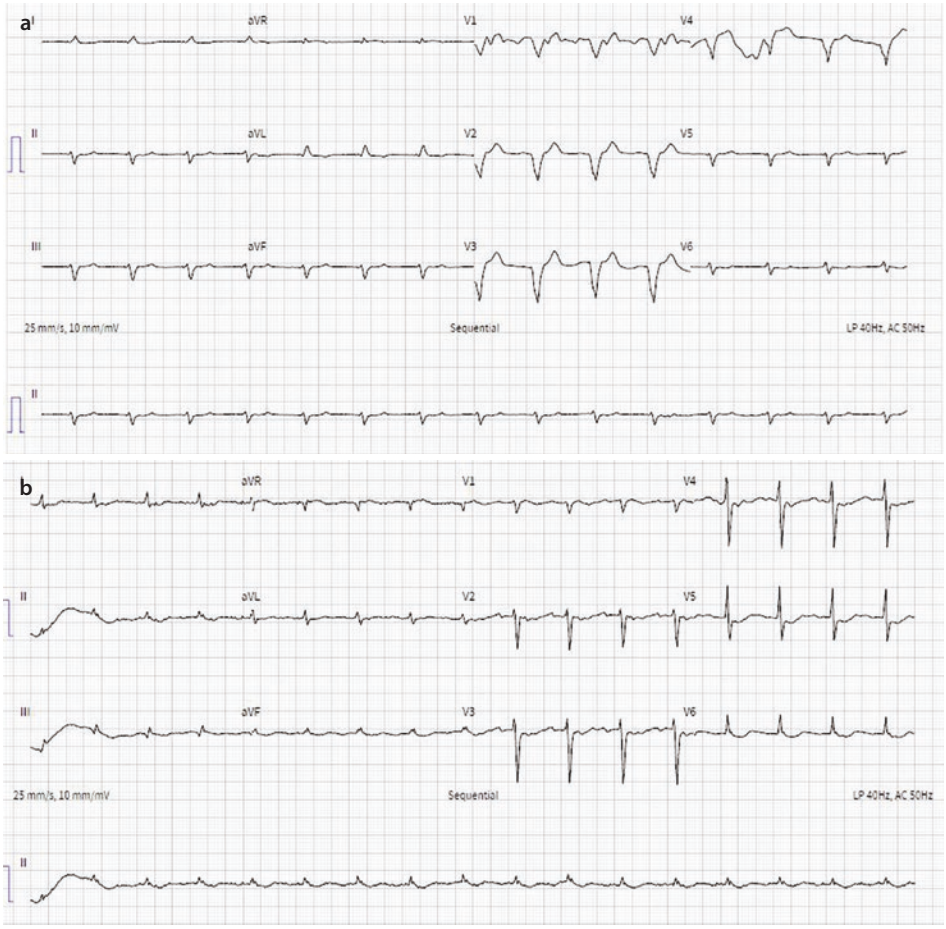

Fig. 31.1 **a** Paced ventricular rhythm at rate 90/min following insertion of single-chamber VVI permanent pacemaker. **b** 12-lead ECG following administration of digoxin-specific antibody fragments

31.3 Differential Diagnosis

On arrival to the critical care unit, our underlying unifying diagnosis remained broad and included all causes of complete heart block.

Whilst awaiting admission bloodwork, a formal collateral history was taken from the patient's daughter. Despite the patient himself stating on admission that he felt well, his daughter mentioned a prodrome of several weeks of intermittent episodes of dizziness occurring unprecipitated. None had resulted in falls or collapse. She further mentioned several days of her father having difficulty driving due to altered vision and varied colour perception. Moreover, she confirmed recent reintroduction of spironolactone following a previous suspension due to a drug-induced acute kidney injury. No other history of note was elicited, and no other recent medication changes had occurred.

Variable	Reference Range	Baseline	Day 0	Day 1	Day 4
Haemoglobin (g/L)	130-170	119	105	82	97
White cell count (x10^9/L)	4-11	5.9	7.8	7.8	4.9
Platelet count (x10^9/L)	150-400	150	189	136	176
Sodium level (mmol/L)	135-150	138	135	139	135
Potassium level (mmol/L	3.5-5.0	4.3	5.2	4.3	4.0
Urea (mmol/L)	3.0-9.2	4.8	9.3	7.6	5.3
Creatinine (μmol/L)	64-104	58	109	81	66
eGFR (mL/min)		90	54	77	85
Total bilirubin level (μmol/L)	0-21	8	7	13	9
Alanine aminotransferase level (IU/L)	10-45	29	36	21	39
Alkaline Phosphatase level (IU/L)	30-130	220	297	188	282
Albumin (g/L)	32-50	32	33	34	30
Digoxin Level (nmol/L)	1.0-2.0	-	4.7	-	-
Troponin I (ng/L)	<34	-	18	-	-

Fig. 31.2 Laboratory data

Blood tests confirmed an acute kidney injury with modest hyperkalaemia. The troponin I level was unremarkable. Other laboratory test results are shown in Fig. 31.2.

Given the prodromal history, recent reintroduction of spironolactone, and acute kidney injury on admission, the working differential diagnosis at this point was chronic digoxin toxicity. This was confirmed when the plasma free digoxin level returned at 4.7 nmol/L (reference range < 2 nmol/L).

31.4 Treatment

In addition to insertion of single-lead VVI Medtronic® permanent pacemaker, the patient was managed with intravenous administration of 80 mg (2 vials) of digoxin-specific antibody fragments, optimisation of fluid-balance and electrolyte status, as well as drainage of the remaining ascites. His digoxin and spironolactone were suspended. The patient remained mechanically ventilated overnight on low-dose vasopressor support before being successfully extubated and weaned off vasopressor support the next morning.

Despite the availability of an effective antidote against digoxin in the form of digoxin-specific antibody fragments, exact indications for its use remain rather uncertain. Moreover, the cost of digoxin-specific antibody fragments (approximately £750 per vial, with often multiple vials needed for treatment) has limited its use in all but

the most life-threatening toxidromes. Current accepted criteria for administration of digoxin-specific antibody fragments are as follows [2]:

- Cardiopulmonary arrest
- Fluid-refractory shock
- High-grade symptomatic atrioventricular block
- Ventricular dysrhythmias
- Potassium level > 5 mmol/L in acute digoxin overdose
- Digoxin level > 12 ng/mL in acute digoxin overdose
- Acute ingestion >10 mg digoxin in an adult (or >4 mg in a child)
- Symptomatic digoxin toxicity with renal dysfunction in chronic digoxin overdose (irrespective of level)

Digoxin-specific antibody fragments have an extremely high affinity for binding digoxin. The result is the formation of inactive complexes within the extracellular space that prevents digoxin from binding the Na+/K+ -ATPase receptor site. Moreover, it creates a high concentration gradient that aids in the extraction of digoxin from the intracellular space. The inactive digoxin-bound digoxin-specific antibody fragments are thereafter renally excreted.

31.5 Evolution, Outcome, and Follow-Up

The patient progressed well. Within 1 h of administration of digoxin-specific antibody fragments, he had regained an intrinsic cardiac rhythm at a rate above that of his pacemaker, and 12-lead ECG demonstrated a sinus rhythm at 100 beats/min (◘ Fig. 31.1b). He was extubated on day 1 following his admission to critical care, neurologically intact, with no ongoing organ support requirement. His acute renal injury resolved. He was independently mobile around the unit. He was discharged to the liver ward on day 2 and discharged from the hospital on day 4 following admission.

On discharge from the hospital, the patient's digoxin remained indefinitely suspended, the spironolactone was reintroduced at a lower dose (50 mg once a day), and his apixaban was restarted. Other medications remained as prescribed on admission.

The patient has subsequently remained well, receiving ongoing monthly abdominal paracentesis for diuretic-refractory ascites. He has received follow-up in the pacemaker clinic, and interrogation of his pacemaker has revealed no further bradycardic episodes. In fact, his rhythm has been predominantly atrial fibrillation with (at times) rapid ventricular response, for which reason his carvedilol has been uptitrated.

31.6 Discussion

We describe a case of digoxin-induced cardiopulmonary arrest supported with mechanical chest compressions and transcutaneous pacing until definitive treatment with transvenous pacing and digoxin-specific antibody fragments. It represents one of only very few cases in the literature of survival with good functional outcome following digoxin-induced cardiopulmonary arrest, with the common treatment in these cases being early administration of digoxin-specific antibody fragments [3].

The case raises points of interest for the critical care physician. In our case, we found that such was the rapid efficacy of digoxin-specific antibody fragments that it made insertion of a permanent pacemaker a potentially unnecessary intervention. It would be our suggestion that in such cases, where pacing is required for unstable bradydysrhythmias, it be managed with a temporary transvenous pacing wire whilst the digoxin-specific antibody fragments take their pharmacological effect.

We further address the question of optimal pad positioning in the context of transcutaneous pacing. The evidence is sparse, though the available literature does suggest that the mean transthoracic impedance is significantly lower when pacing pads are sited in the antero-posterior configuration when compared with the antero-lateral configuration [4]. The current position of the American Heart Association and the European Society of Cardiology states that 'the superiority of one position over another has not been established'. However, as seen in our case, where transcutaneous pacing fails to obtain capture in one of the configurations, it is important to trial the alternative position, as this may still be successful.

Finally, we consider the use of mechanical cardiac support in the context of digoxin-associated cardiopulmonary arrest. There is a limited, though growing, evidence base to support its use in the context of acute cardiogenic shock in the context of life-threatening poisonings. However, the common feature in these toxins is the absence of ready reversibility of the toxic agent. This is not the case with digoxin toxicity where digoxin-specific antibody fragments are available. A review of the literature revealed a single case report where VA-ECMO has indeed been trialled in the context of digoxin-associated cardiopulmonary arrest. This was in the context of lack of immediate availability of digoxin-specific antibody fragments and was not associated with survival of the patient to discharge [5]. The present evidence does not support use of mechanical cardiac support in the context of digoxin-induced cardiogenic shock, and certainly not in preference to digoxin-specific antibody fragments. However, mechanical cardiac support does remain a potential option in the context of refractory shock associated with mixed poisonings or of poisonings without antidote availability [6].

Take-Home Messages

- Cardiac glycosides, whilst retaining a limited clinical use in management of patients with congestive cardiac failure, have a narrow therapeutic window and toxic side effects that include cardiac dysrhythmias, gastrointestinal side effects, electrolytic disturbances, and visual side effects including xanthopsia.
- Small decrements in creatinine clearance can result in significant increases in plasma digoxin level and inadvertent digoxin toxicity.
- Cardiac compressions, positive chronotropes, and temporary pacing may be required in the context of high-grade bradydysrhythmias associated with digoxin toxicity but should not delay early empiric use of digoxin-specific antibody fragments.

Summary

An 83-year-old man presented to the gastroenterology day unit for an elective abdominal paracentesis. His background was notable for Child-Pugh B hepatic cirrhosis and atrial fibrillation for which he took digoxin and carvedilol. Spironolactone was recently reintroduced for management of his ascites, following which the patient noted a prodrome of several weeks of intermittent dizziness, and prior to admission, a few days of altered colour vision.

On the day of admission, following an uneventful abdominal paracentesis, the patient collapsed and suffered a bradyasystolic cardiopulmonary arrest. Signs of life returned after approximately 45 s of cardiopulmonary resuscitation, and the patient was found to be in a critically unstable complete heart block with a ventricular rate of 12 beats/min. Failed attempts at pharmacological management with positive chronotropes was followed by successful transcutaneous pacing with return of haemodynamic stability. In discussion with our cardiology colleagues, it was agreed to proceed to emergent insertion of a single-lead VVI permanent pacemaker device.

His underlying rhythm at this time had degenerated into a P-wave asystole and was entirely pacemaker dependent. His blood results on arrival in the critical care unit demonstrated an AKI with mild hyperkalaemia (5.2 mmol/L), and a raised digoxin level of 4.7 nmol/L (reference range < 2.0 mmol/L). The patient was subsequently treated with 80 mg of digoxin-specific antibody fragments, following which he had a notable rhythm change from a ventricularly paced rhythm at rate 90, to an independent sinus rhythm of rate 100. This occurred within 1 h of administration of digoxin-specific antibody fragments.

The patient's digoxin was permanently withheld, and he made an excellent recovery. He was extubated (neurologically intact) on day 1 post cardiopulmonary arrest and discharged home on day 4 of his hospital stay. As of writing his case report, the patient remained well and functionally independent at home.

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Cardiac Arrest: Pediatric Out-of-Hospital Cardiac Arrest on the Soccer Pitch—How Implementation of Digital Solutions into the Chain of Survival Can Help with a Favorable Outcome

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Contents

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Learning Objectives

- Relevance of the chain of survival for survival and favorable neurological outcome in Pediatric Out-of-Hospital Cardiac Arrest
- Smartphone-based applications for early commencement of high-quality CPR after sudden Out-of-Hospital Cardiac Arrest
- Differentiated recruitment of available resources to improve processes and increase chances for a favorable neurological outcome in cardiac arrest situations

32.1 Introduction

Rates of survival to hospital discharge of patients with out-of-hospital cardiac arrest (OHCA) range below 10% [1]. Pediatric OHCA (POHCA) is very rare and survival rates are also very poor. Besides this, many of the few surviving children suffer from new severe neurological impairments.

Improved survival and an increase in a favorable neurological outcome after cardiac arrest could be observed when high-quality cardiopulmonary resuscitation (CPR) by witnessing bystanders was started within the very first minutes after the collapse [2]. The case of Christian Eriksen, midfielder of the Danish national soccer team who suffered a sudden cardiac arrest during a game of UEFA EURO 2020 witnessed by millions on television, might serve as a blueprint for successful resuscitation after cardiac arrest if response times are short and CPR commences immediately. However, for regular Emergency Medical Services, it is impossible to achieve such short response and arrival times. Therefore, after implementing emergency medical dispatcher-assisted (telephone) CPR in pre-hospital emergency medicine, modern concepts started to incorporate smartphone-based activation of community first responders to OHCAs [3].

The following case of a POHCA on the soccer pitch illustrates successful resuscitation due to a perfectly orchestrated chain of survival including a smartphone-based activation of a medically trained first responder to commence high-quality CPR until Emergency Medical Services and highly trained medical professionals arrived on scene.

Case Presentation

On a summer evening in August, a 7-year-old boy collapsed on the soccer field during soccer training of his school team. Recognizing unresponsiveness and apnea, the coach of the team dispatched an emergency call promptly from the pitch. The emergency medical dispatcher of the Berlin Fire Brigade control center recognizing the cardiac arrest situation guided the bystanding coach of the patient's soccer team into a dispatcher-assisted CPR. In parallel, professional Emergency Medical Service of the Berlin Fire Brigade was alarmed and the smartphone-based application for civilian resuscitation in the vicinity (KATRETTER©) was activated for the area of the emergency scene. Due to the location of the emergency scene, a fire engine equipped with six fire fighters,

some of them also trained as paramedics, with an estimated arrival time on scene of 4 min was alarmed as first responder. Consecutively, an ambulance equipped with two paramedics and an emergency vehicle equipped with a paramedic and an emergency physician were sent out, both with an estimated arrival time of 8 min. The information of the established dispatcher-assisted CPR was texted to all alarmed fire brigade engines on route.

When the call of the smartphone-based application was activated, by chance, a member of the volunteer Berlin Fire Brigade was passing the sports fields. Arriving less than 3 min after the collapse on scene, he started to establish basic life support with high-quality CPR. The members of the fire engine were second to arrive on the field and took over basic life support with high-quality CRP and bag-mask ventilation including administration of oxygen. Chest compressions and ventilation via a bag-valve-mask were carried out in a 15:2 ratio. Paramedics and emergency physician arrived simultaneously around 10 min after the arrest and measures were extended to advanced cardiac life support. The immediately established ECG monitoring showed, although obscured by artifacts, a pulseless electric activity. With an estimated body weight of 30 kg, 300 µm of epinephrine were administered through a rapidly established intravenous access. After the respective CPR cycle, ECG monitoring showed ventricular fibrillation and was immediately treated with a defibrillation shock of 120 Joule.

During the second CPR cycle, the father of the patient was present on the soccer field and reported that he himself suffers from hypertrophic cardiomyopathy similar to his mother and his grandmother who both died of sudden cardiac death at early age. Given the sudden collapse during exercise, the detected arrhythmias, and the family history, an inherited structural cardiac disease such as a hypertrophic cardiomyopathy moved high on the list of possible differential diagnoses for the reason of this cardiac arrest. With a specialized pediatric heart center in the northwest of Berlin and considering the current rush-hour traffic conditions and the appropriate helipad-like landing conditions of a soccer field, the emergency physician opted for a follow-up alarm of the emergency-rescue helicopter.

At the end of the CPR cycle after the defibrillation shock, the patient showed movements of his limbs and return of spontaneous circulation (ROSC) was detected. Therefore, ROSC was achieved around approximately 15 min of CPR. Complete hemodynamic monitoring was established and the boy was transferred into the ambulance. He reacted with withdrawal from painful stimuli and incomprehensible sounds. In coma post resuscitation, the patient was again sedated with fentanyl and propofol and including usage of rocuronium for muscle relaxation, he was intubated and mechanically ventilated. At the time of intubation, the boy had received 250 mL of balanced electrolyte solution. Meanwhile the helicopter had landed on the soccer field and the now hemodynamically stable patient was transferred by air transport to the German Heart Center Berlin and admitted to the Pediatric Intensive Care Unit (PICU).

32.2 Investigations

Because the father of the patient was allowed to accompany the helicopter transfer, a detailed family history could be taken in parallel to the admission to the PICU. This history again confirmed a high suspicion for an inherited structural cardiac disease, namely, a hypertrophic cardiomyopathy, as underlying disease and potential reason for the cardiac arrest.

The 12-lead ECG on admission showed a sinus rhythm; signs of biventricular hypertrophy; deep Q waves in leads II, III, and aVR; negative T waves in leads V3–V6; and ST elevations in leads V1 and 2. Transthoracic echocardiography was performed and revealed a global concentric hypertrophy with a diastolic septum diameter of up to 19 mm. The ejection fraction appeared reduced at 38% but improved to 46% upon the administration of low-dose noradrenaline (Fig. 32.1). In addition, a second degree mitral valve regurgitation was detected. In the chest X-ray, an enlarged cardiac silhouette was displayed (Fig. 32.2). No further pulmonary or cardiac pathologies could be identified radiologically.

The first capillary blood gas analysis indicated a combined metabolic and respiratory acidosis with a pH value of 7.226, a paCO2 of 49.6 mmHg, a base excess of −7.1, and a serum lactate of 47 mg/dl. Laboratory findings included elevated values for myoglobin (233 µg/L), troponin (245 ng/L), creatinine kinase (377 U/L), creatinine phosphokinase MB (58.9 U/L), and lactate dehydrogenase (432 U/L) as well as a mild thrombocytopenia (163 /nL).

A coronary angiogram on the day following admission showed a recovering left ventricular ejection fraction measured at >55%. The mitral valve regurgitation was not detectable anymore. There were no pathologies regarding coronary perfusion and no signs for a left ventricular outflow tract obstruction detected.

After extubation on ICU day 2 after the cardiac arrest, multiple neurological examinations could not detect any neurological deficit. A cranial MRI was performed on day 4 after admission revealing no intracranial pathology and no single sign of past hypoperfusion or hypoxic damage.

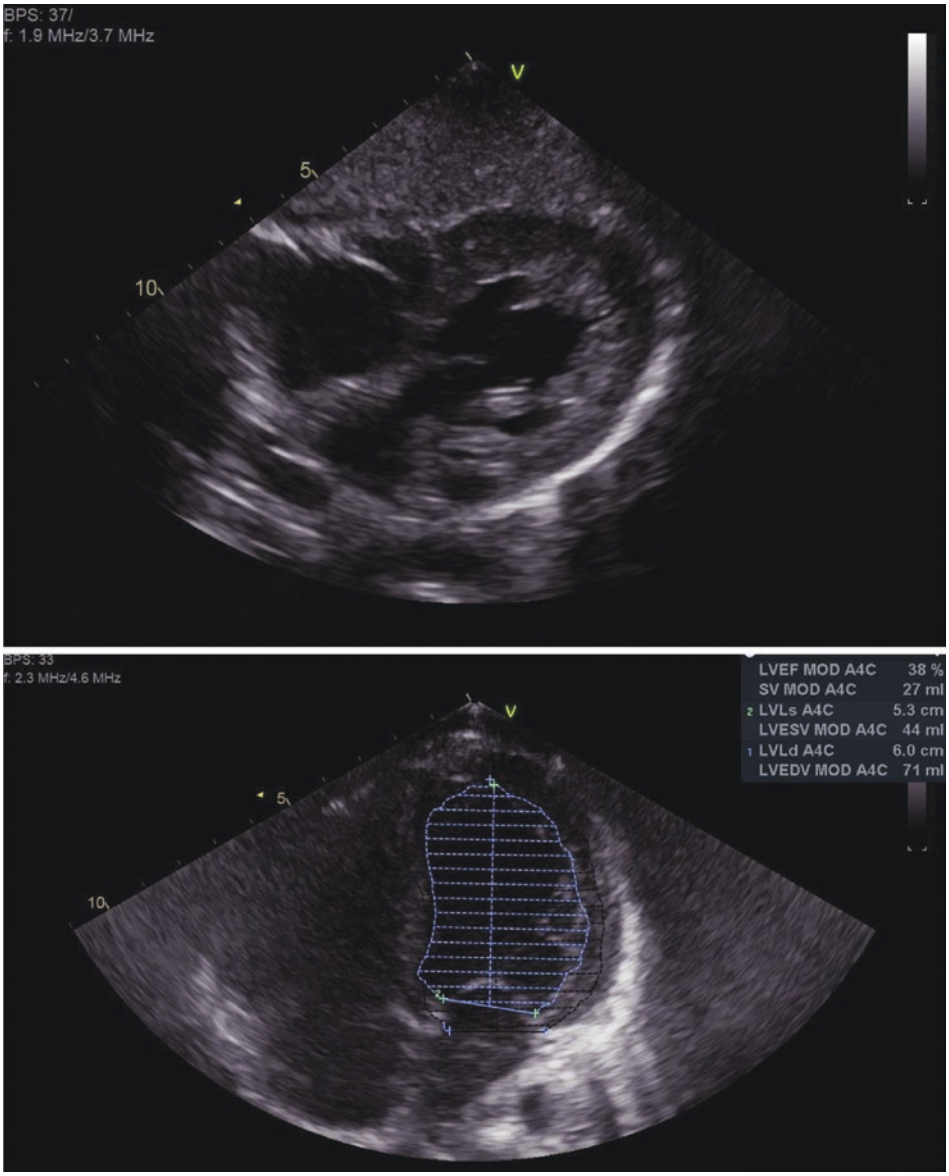

Fig. 32.1 Transthoracic echocardiography on admission to ICU showing the hypertrophic left ventricle (upper panel) and a reduced ejection fraction (lower panel)

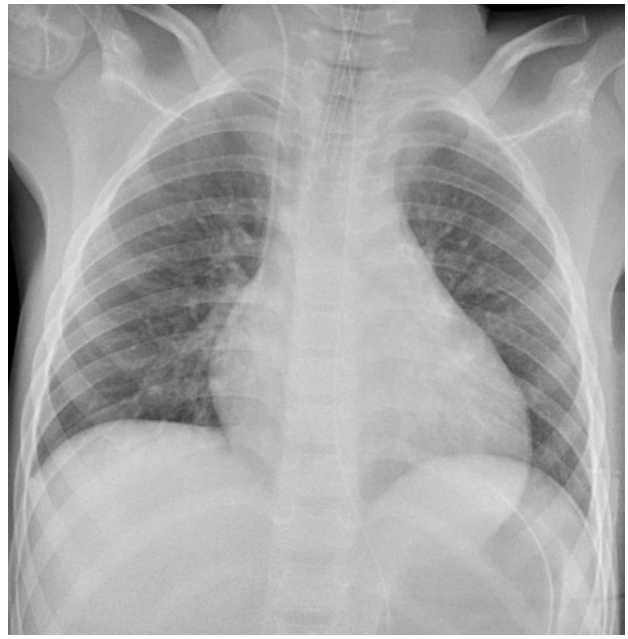

Fig. 32.2 Chest X-ray on admission to ICU depicting signs of cardiomegaly

32.3 Differential Diagnosis

Based on the family history reported promptly by the father, from early on, the cause of the cardiac arrest appeared plausibly linked to a hypertrophic cardiomyopathy. The immediate workup of the emergency physician to detect any of the reversible causes for the cardiac arrest by evaluation of acute medical history and clinical examination could quickly rule out hypoxia, hypovolemia, hypo- or hyperthermia, toxins, or a tension pneumothorax. Hypoglycemia was excluded by on site measurement of capillary blood glucose levels. Upon ROSC and a stabilizing hemodynamic situation in the further course, a significant pulmonary embolism or pericardial tamponade remained very unlikely and echocardiography on admission to PICU did not demonstrate any signs for either of those both pathologies. On the bottom of the detailed family history, echocardiography on admission secured the diagnosis of a hypertrophic cardiomyopathy. Coronary angiography finally could exclude a left ventricular outflow tract obstruction and therefore the diagnosis of a hypertrophic nonobstructive cardiomyopathy was confirmed.

32.4 Treatment

Upon arrival at the German Heart Center Berlin, the patient was directly admitted to the PICU and the abovementioned investigations were performed. Sedation and mechanical ventilation were continued. A central venous catheter was introduced in the right interior jugular vein. The patient then received milrinone and noradrenaline

for hemodynamic support. With stabilizing hemodynamics, both drugs could be weaned over the further course on the PICU. Early enteral nutrition was administered via a nasogastric tube. Targeted temperature management was initiated with normothermia as a goal. When the coronary angiogram confirmed the diagnosis of a hypertrophic cardiomyopathy without coronary perfusion problems or signs for a left ventricular outflow tract obstruction, the patient was weaned from sedation and extubated on ICU day 2. The patient showed disoriented phases in the initial period after extubation. Cranial MRI and EEG showed no pathologic findings, and frequent neurological exams could not detect any neurological defect. Therefore, disorientation was most likely associated with critical illness delirium. After intermittent treatment of disturbances of the circadian rhythm with oral melatonin, cognitive function was fully restored shortly after. Shortly after admission, the patient developed a community-acquired pneumonia which was empirically treated with ampicillin/sulbactam. Inflammation markers decreased rapidly and bacterial culture revealed the growth of MSSA, *Haemophilus influenzae*, and *Streptococcus pneumoniae* in the tracheobronchial secretions. Anti-infective therapy was completed after 7 days of successful pneumonia treatment. Following complete recovery from infection, an implantable cardioverter defibrillator was inserted into a subcutaneous pouch and set to administer a shock of 41 Joule in case of a heart rate > 190 bpm and to pace in the event of a heart rate < 40 bpm. Pharmacological tertiary prevention was established by oral medication with metoprolol (18.75 mg twice a day) and potassium (20 mmol/day).

32.5 Evolution, Outcome, and Follow-Up

The young patient was discharged home on day 9 after the cardiac arrest. A follow-up stay in a neurorehabilitation unit was not necessary due to a complete normal neurological status after multiple neurological examinations and tests. According to information obtained from the father, the boy was back to school the following week and took part in all educational activities except for sports.

In the further course, clinical status and ICD function was monitored regularly. No episodes of ventricular fibrillation have been recorded thus. Metoprolol dosage was readjusted to 2 mg/kg to match the gradually increasing body weight of the normally developing child. A follow-up echocardiogram showed a regular heart function and no pathologies except for the signs of a hypertrophic myocardium.

The parents reported no cognitive disorders in their son. Their child would continue his scholarly education without adversities. A couple of months later, he and his family visited the local fire brigade station and met the healthcare providers that were involved in his preclinical rescue while the father admitted that he would consider to become a volunteer fire fighter.

32.6 Discussion

In addition to the importance of teamwork and resource management in emergency situations, this case demonstrates how modern concepts with the usage of digitalization can further improve components to perfect the chain of survival. While multiple types of personnel and levels of medical training were involved and collaborated efficiently, a key component of this successful POHCA was certainly the early commencement of high-quality CPR provided by a nearby located and trained first responder who was alerted by an alarm via a smartphone-based application.

The current smartphone application used by the Berlin Fire Brigade Control Center was developed based on findings of the Fraunhofer Institute for Open Communication Systems, Berlin, which is part of the Fraunhofer German research organization focusing on application-based research. The free application "KATRETTER©" can be installed by anybody who would like to assist in case of an emergency. Potential helpers can enlist themselves as civilian rescue aids with or without medical experience and will be alerted once an emergency call with a probable resuscitation effort is transmitted close to their current location. They can then respond to the alert or report to be unavailable.

The European Resuscitation Council strongly recommends the notification of citizens willing to engage in resuscitation efforts by smartphone applications in the 2021 guidelines [4]. The council bases their recommendation on multiple surveys. A systematic review of international studies found that first responders intervened in 28.7% of alerts and arrived at the scene earlier than the professional team in 47% of cases [5]. Until now, there is scarce research on the topic of medical outcome of patients who first received CPR by volunteers alerted via smartphone applications versus professional first responders. However, first results are promising and concordant to data obtained for early CPR by bystanders in OHCA [6]. Whether the evidence obtained for smartphone-based activation of community first responders to adult OHCA can be easily transferred to POHCA remains currently unknown.

Regarding the concept of the chain of survival, this case illustrates nicely how a functioning and well-interlinked teamwork effort leads to a favorable outcome in a POHCA and at the same time, it highlights that functioning of every part of this chain is crucial for its integrity.

Taken together, digital solutions to assist emergency medicine and resuscitation efforts in OHCA for a favorable outcome have great potential and further exploration is needed. A widespread network of digitally interconnected first responders is a highly valuable resource and a support system with great potential for timely and high-quality treatment of critically ill patients.

Take-Home Messages

- Perfect execution of the chain of survival allows survival and favorable neurological outcome in Pediatric Out-of-Hospital Cardiac Arrest.
- Implementation of smartphone-based applications can close the time window until commencement of high-quality CPR after sudden Out-of-Hospital Cardiac Arrest.
- Differentiated recruitment of available resources straightens processes and increases chances for a favorable neurological outcome after cardiac arrest situations.

Summary

Pediatric out-of-hospital cardiac arrest (POHCA) is rare and survival rates are poor. Improved survival and increased favorable neurological outcome after OHCA was observed when bystanders started high-quality cardiopulmonary resuscitation (CPR) within the very first minutes after the collapse. Therefore, modern concepts commenced to incorporate smartphone-based activation of community first responders to OHCAs.

Here we report the case of a 7-year-old boy who collapsed on the soccer field during soccer training. Besides alarming the Emergency Medical Services, the Fire Brigade Control Center forwarded the emergency call to users of a smartphone-based application for civilian resuscitation in the vicinity. A thus informed helper, coincidentally passing the soccer fields, initiated high-quality CPR. The subsequently arriving professional emergency medical teams were able to successfully resuscitate the young patient and—after learning he suffered from hypertrophic cardiomyopathy—transferred him to a specialized cardiac center. There, he received an implantable cardioverter defibrillator and recovered from the event without any neurological deficit.

This case demonstrates how modern digital solutions can assist in OHCA to achieve a favorable outcome. A widespread network of digitally interconnected first responders is a highly valuable support system with great potential for timely and high-quality treatment of critically ill patients in the community.

Acknowledgements Emergency medicine and in particular cardiac arrest situations are always team efforts. Therefore, we are tremendously thankful for all involved in the therapy of this young patient. For the preclinical treatment, we express our gratitude to the members of the Berliner Feuerwehr (Berlin Fire Brigade) including the emergency medical dispatcher of the Berlin Fire Brigade control center, the first responder of the volunteer Berlin Fire Brigade, and the crews of the involved fire engine, ambulance, and emergency vehicle of the Berlin Fire Brigade.

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Principles and Management of Heart Failure and Cardiogenic Shock

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Contents

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Learning Objectives

- Emphasize the severity of acute, decompensated heart failure regarding readmission and mortality rates
- Describe the causes of acute heart failure and define systolic versus diastolic heart failure
- Describe the physiology, surgical management, and emergency percutaneous procedures of valvulopathies
- Summarize the definition, diagnosis, and treatment of cardiogenic shock

33.1 Introduction and Acute Heart Failure: Systolic and Diastolic Dysfunction

Acute heart failure (HF) is responsible for more than one million hospitalizations annually in both the United States and Europe. Although the outcomes for ambulatory patients with HF have improved with the discovery of evidence-based therapies, hospitalized patients continue to experience high post-discharge mortality and readmission rates. The first appearance of acute, decompensated HF often marks the beginning of a progressive decline in clinical status [1].

HF is not a single entity, but it is usually classified according to the portion of cardiac cycle that is affected (systolic or diastolic dysfunction) and the side of the heart that is involved (right-sided or left-sided HF) [2]. This chapter describes the basic principles and management of HF and cardiogenic shock. The most common causes of acute HF in the intensive care unit are summarized in Table 33.1.

33.1.1 Systolic and Diastolic Dysfunction

Left ventricular (LV) failure can be divided into systolic and diastolic dysfunction. The former is characterized by a reduced ejection fraction and an enlarged LV cham-

Table 33.1 Causes of acute heart failure

Coronary artery disease
Cardiac arrhythmias
Infection (sepsis, myocarditis)
Mechanical (endocarditis, pulmonary embolism, valvulopathies, cardiac tamponade)
Drugs
Hypoxemia
Metabolic (acidemia, electrolyte disturbances, thyrotoxicosis)
Myocardial contusion (trauma)
Myocardial infiltration (tumor, sarcoidosis, amyloidosis)
Neuromuscular conditions (Duchenne muscular dystrophy, Friedrich ataxia, myotonic dystrophy)

Table 33.2 Measures of left ventricular (LV) performance in systolic and diastolic heart failure

LV performance measure	Systolic heart failure	Diastolic heart failure
End-diastolic pressure	>16 mmHg	>16 mmHg
End-diastolic volume	>97 mL/m^2	≤97 mL/m^2
Ejection fraction	<45%	>50%

ber and the latter by an increased resistance to filling with increased filling pressures [3]. Echocardiography is the most relevant technique for noninvasive differentiation of the two forms.

Systolic dysfunction results in an increase in end-diastolic volume and diastolic dysfunction results in a decrease in end-diastolic volume. The proposed diagnostic criteria and threshold values for identifying systolic vs. diastolic dysfunction [4] are summarized in Table 33.2.

Many cases of HF have some degree of systolic and diastolic dysfunction; hence the terms systolic heart failure and diastolic heart failure are considered obsolete. Therefore, HF that is predominantly the result of systolic dysfunction is called HF with reduced ejection fraction and HF that is predominantly the result of diastolic dysfunction is called HF with preserved (or normal) ejection fraction.

33.2 Valvulopathies

Acute heart failure and cardiogenic shock secondary to a valvulopathy require early identification in order to guide management. Left-sided valvulopathies are most common, and these can then progress to cause acute heart failure or cardiogenic shock. In developed countries, aortic stenosis is the most likely cause, followed by mitral regurgitation, aortic regurgitation, and then mitral stenosis. These patients may present when a chronic condition reaches a critical point or clinical deterioration is caused by a concurrent illness. Additionally, acute valvulopathies resulting in heart failure may be secondary to infection with infective endocarditis, ischemia which mostly commonly causes mitral regurgitation, or traumatic causes such as aortic dissection resulting in aortic regurgitation [5].

The management of these conditions varies. In the event of decompensation of a chronic condition, management frequently focuses on treatment of the cause of decompensation while ensuring cardiac output and oxygen delivery is maintained. For an acute valvulopathy associated with hemodynamic implications, the gold standard for treatment is early surgical management with use of mechanical cardiac support as required.

33.2.1 Physiology of Valvulopathy

When considering hemodynamic support, the physiology associated with the valvulopathy needs to be understood.

Aortic stenosis causes a progressive LV outflow obstruction with resultant increase in LV systolic pressure. This causes LV hypertrophy and diastolic dysfunction with both an increased myocardial oxygen demand and decreased supply. As decompensation occurs, prevention of pulmonary congestion is reliant on the patient being in sinus rhythm and preload maintained. Maintenance of diastolic pressure is critical to avoid subendocardial ischemia. Intravenous fluids may be required to maintain preload. In the presence of cardiogenic shock, both noradrenaline and nitroprusside can be considered with inotropic agents being used in the presence of LV impairment [6].

In mitral stenosis, compensation occurs with left atrial dilatation. Often patients can compensate for a number of years and remain asymptomatic. Symptoms develop when pulmonary hypertension develops with subsequent pulmonary edema. This may be precipitated by the development of atrial fibrillation. Atrial fibrillation reduces diastolic time which further increases atrial pressure. Pregnancy may also cause decompensation of previously stable mitral stenosis due to an increased circulating blood volume that overwhelms the compensatory mechanisms. When considering hemodynamic support in mitral stenosis, it is important to maintain a low to normal heart rate, in sinus rhythm, where possible to ensure sufficient time in diastole. Normovolemia will help maintain an adequate preload. Systemic vascular resistance must be maintained to prevent a fall in coronary perfusion. Noradrenaline may be required to do this [7].

In mitral regurgitation, atrial dilatation occurs due to the increased atrial blood volume with the retrograde movement during regurgitation. If the mitral regurgitation has occurred acutely due to infection, or ischemia with chordae rupture, this is more likely to cause decompensation with symptomatic pulmonary hypertension. Nitrates or diuretic administration may help to reduce the filling pressure. Afterload reduction is also important; this may require use of inodilators or use of mechanical support, which will be discussed later [7].

If chronic, aortic regurgitation causes a compensatory left ventricular hypertrophy and dilatation to accommodate the increased ventricular volume. A fall in preload may affect these compensatory mechanisms. The regurgitation also causes decreased diastolic pressure with reduced coronary blood flow. If aortic regurgitation has occurred acutely due to either infection, aortic dissection, or trauma, these compensatory mechanisms do not exist and these patients are likely to present in acute heart failure with both systemic hypotension and pulmonary edema. Noradrenaline may be required to support the patient to definitive management [5].

33.2.2 Surgical Management

Surgical management of symptomatic valvulopathies remains the most effective treatment. Open procedures used to be the standard for all patients, but with the evolution of percutaneous procedures, this is changing. The decision may be guided

by a number of factors including a patient's co-morbidities as well as technical factors, for example, calcification of the valve. The surgical options have also evolved. Historically all operations required a midline sternotomy but minimally invasive techniques are now common with mitral valve repair or replacement performed via a right thoracotomy, for example [7].

33.2.3 Emergency Percutaneous Procedures

Transcatheter cardiac valve procedures have also developed over recent years. This includes balloon valvuloplasty which can be used in the management of both aortic and mitral stenosis. The first procedure was performed over 30 years ago. This is used in the highest-risk patients; it may be a life-saving procedure for patients with cardiogenic shock secondary to valvular stenosis who are felt too high risk for transcatheter valve replacements or open surgery. However, it is associated with a number of complications including aortic regurgitation, subsequent myocardial dysfunction, cerebrovascular events, and a high restenosis rate, which is quoted as up to 70%. One study showed a 1-month mortality of 47% and 1-year of 70%. If it is to be performed, it should be done early as the lowest mortality has been associated with the procedure being performed before vasoactive drugs are required or within 48 h of the onset of cardiogenic shock. A definitive second procedure should be performed at a later date, for patients who have had an emergency balloon valvuloplasty [5].

Transcatheter valve implantation for aortic stenosis has been associated with a better short-term mortality than balloon valvuloplasty followed by a later transcatheter valve implantation, even in frail patients. Transcatheter valve implantation requires passing a wire across the valve, balloon valvuloplasty, and then deployment of a prosthetic valve. It may be performed for aortic stenosis, regurgitation, or mitral stenosis and can have similar mid-term outcomes to open cardiac procedures and is associated with fewer immediate complications. Complications that should be considered include a requirement for post-procedure pacing, with aortic valves. The incidence of perioperative stroke is quoted as 5% and vascular complications related to the access sites as high as 10–15% [6].

Mitral regurgitation may be managed with a MitraClip® procedure. This device clips two leaflets of the mitral valve together. This is a procedure considered for high risk patients and has a 20% failure rate [7].

33.3 Cardiogenic Shock and Mechanical Cardiac Support

33.3.1 Definition

Although there is some variability in the definition of cardiogenic shock used in different clinical trials, it can be roughly defined as a state of end-organ hypoperfusion due to cardiac failure [8]. Patients present with systemic hypoperfusion that manifests with altered mental status, cool skin, increased capillary refill time, and oliguria, with or without hypotension.

Hemodynamic monitoring has been used to define cardiogenic shock. Historically, it has been represented by low cardiac index, elevated systemic vascular resistance, and a high pulmonary capillary wedge pressure (PCWP). However, recent trials have expanded cardiogenic shock hemodynamic profiles; all possible phenotypes are characterized by low cardiac index, but ventricular preload, volume, and systemic vascular resistance may vary [9].

33.3.2 Etiology and Outcomes

The most common cause of cardiogenic shock is acute myocardial infarction, complicating 5–10% of all cases [10]. It is caused by the loss ventricular myocardium or mechanical complications such as free wall rupture, ventricular septal defect, and papillary muscle rupture. In patients with chronic ventricular dysfunction, it may present as acute decompensated heart failure with cardiogenic shock. Other less frequent causes of cardiogenic shock may be valvular disease, myocarditis, congenital lesions, pericardial diseases, or direct trauma to the heart. Post-cardiotomy patients are also at risk, triggered by intraoperative complications or predisposing factors, such as inadequate myocardial protection, bypass graft failure, and prosthetic valve dysfunction.

Mortality after cardiogenic shock remains high despite advances in mechanical support, with mortality rates around 35–40% and no intervention apart from culprit vessel revascularization for patients with myocardial infarction demonstrating a survival benefit [11].

33.3.3 Diagnosis and Treatment

Basic 12-lead electrocardiogram, laboratory evaluation, physical examination, and point of care echocardiography may suffice to diagnose cardiogenic shock and need for reperfusion therapy. The Society for Cardiovascular Angiography and Interventions (SCAI) shock stage classification (◘ Fig. 33.1) correlates with mortality risk and can be a helpful tool guiding intervention.

Initial stabilization includes the use of vasoactive and inotropic therapies. Noradrenaline is the preferred first-line agent, and if inotropic support is required, outcomes are similar with dobutamine and milrinone. If the patient is chronically treated with beta-blockers, milrinone or levosimendan is preferred. Inotropic drugs should be used in the lowest possible doses as they may increase myocardial oxygen demand and ischemic burden [13].

Coronary reperfusion is the only evidence-based therapeutic intervention for patients with acute myocardial infarction presenting with cardiogenic shock. Pharmacological therapy with antiaggregant and anticoagulant drugs should be initiated immediately. An early invasive strategy with appropriate revascularization is recommended even in patients with uncertain neurological status or those who have received prior fibrinolysis, regardless of the time delay from myocardial infarct onset. For patients with multivessel coronary artery disease, the 30-day risk of death or renal replacement therapy is lower in those who initially underwent percutaneous

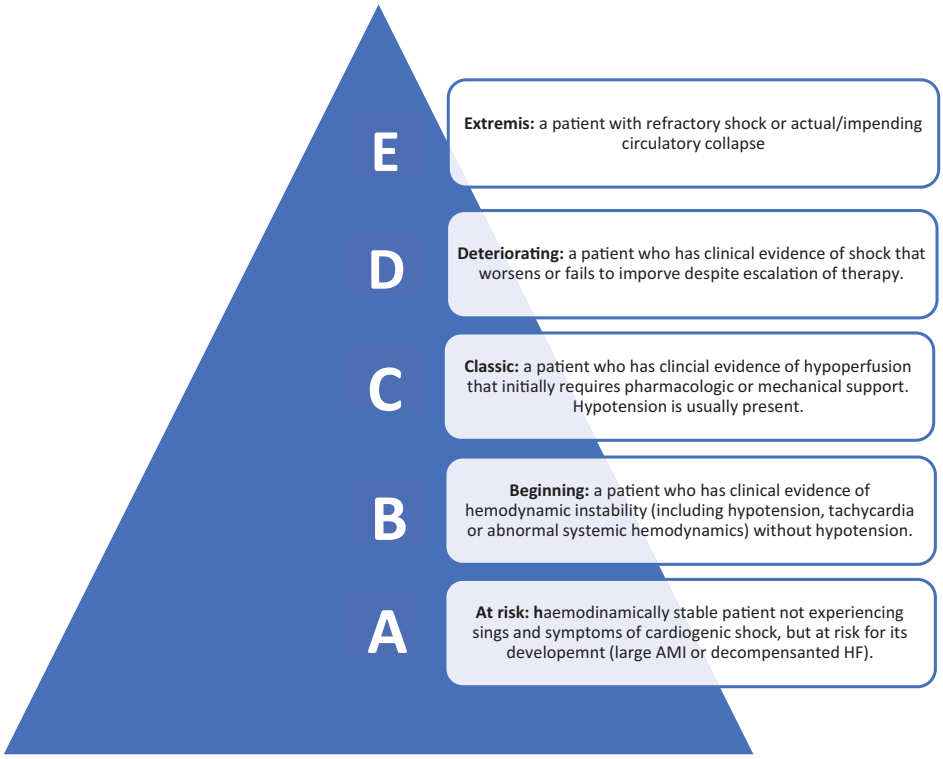

Fig. 33.1 SCAI shock stages. Modified from Naidu et al. 2022 [12]. *AMI* acute myocardial infarction; *HF* heart failure

revascularization of the culprit lesion only than in those who underwent immediate multivessel revascularization [14].

During and after revascularization, hemodynamic status should be monitored using perfusion markers (lactate), serial echocardiograms, or invasive hemodynamic monitoring if available. Mechanical ventilation is often required for the management of pulmonary edema-related hypoxemia, excessive work of breathing, airway protection in case of altered mental status, or electric instability.

For patients deteriorating despite therapy, mechanical circulatory support can be considered, although exactly when to incorporate those devices to shock care is controversial. Mechanical circulatory support devices may be used as a bridge to myocardial recovery or to assess candidacy for a durable ventricular assist device or cardiac transplantation.

33.3.4 Mechanical Circulatory Support Devices

Mechanical circulatory support devices can be inserted percutaneously or surgically and can be broadly classified into temporary or durable. The implantation of durable mechanical circulatory support devices in highly acute patients is associated with lower survival rates compared with more stable patients, so the current recommenda-

tion (both by the American Heart Association and the International Society of Heart and Lung Transplantation) is to implant temporary mechanical circulatory support devices in high-risk patients to allow neurologic assessment and clinical optimization before the consideration of a long-term device.

Temporary mechanical support devices include intra-aortic balloon pump, percutaneous devices such as TandemHeart (Cardiac Assist, Inc., USA) and Impella (Abiomed, Germany) and extracorporeal membrane oxygenation (ECMO). Right ventricle support can be achieved with Impella RP (Abiomed), TandemHeart in a RV support configuration (right atrium to pulmonary artery), or ECMO with a ProtekDuo cannula (TandemLife). Venoarterial ECMO is the preferred option when there is poor oxygenation that is not expected to improve or during cardiopulmonary resuscitation. A summary of the main characteristics of temporary devices can be seen in Table 33.3.

A surgically implanted device can be considered (Centrimag), with inflow cannula placed in the left atrium or left ventricle and outflow cannula in the ascending aorta. For right ventricular support, the inflow cannula is placed in the right atrium and the outflow cannula in the pulmonary artery. Biventricular support can be achieved if necessary.

Table 33.3 Comparison of temporary mechanical circulatory support devices. *RA* right atrium; *PA* pulmonary artery; *Ao* aorta; *LV* left ventricle; *RV* right ventricle; *V* vein; *IJV* internal jugular vein; *FA* femoral artery; *A* artery; *VA* venoarterial

	Impella RP	TandemHeart RA-PA	VA-ECMO	IABP	Impella (CP, 5.5)	TandemHeart LA-FA
Max flow	4 L/min	4 L/min	7 L/min	0.5 L/min	4–5.5 L/min	4 L/min
Mechanism	Axial continuous flow pump (RA to PA)	Centrifugal continuous flow pump (RA to PA)	Centrifugal continuous flow pump (RA to Ao or RA to PA)	Aortic balloon inflation and deflation	Axial continuous flow pump (LV to Ao)	Centrifugal continuous flow pump (LA to Ao, transeptal)
Cannula size	V 22F	IJV 29F	FA 15-17F V 23-25F IJV 29F	A 7-8F	A 14-21F	A 12-19F V 21F
LV unloading	–	–	–	+	++	++
RV unloading	+	+	++	–	–	–
Afterload	–	–	++	–	–	+

If heart function does not recover, cardiac transplantation or implantation of a durable mechanical circulatory support device may be the only hope for survival. Candidacy should be concurrently assessed by an expert team upon implantation of mechanical support.

33.4 Conclusion

Cardiogenic shock is a state of end-organ hypoperfusion due to cardiac failure that is associated with a high morbidity and mortality. Basic examinations facilitate etiological diagnosis. Acute myocardial infarction is the most frequent cause of cardiogenic shock and revascularization therapy the only intervention that has proven a benefit in survival. For patients with cardiogenic shock refractory to conventional measures, mechanical cardiac support can be considered.

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A 60-Year-Old Woman with Gastrointestinal Bleeding in Hemorrhagic Shock: An Unexpected Shift in Shock Etiology

Ola Solli Grude and Pål Klepstad

Contents

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Learning Objectives

- Blood pressure does not equal flow and organ perfusion. Findings such as cold extremities, mottling, prolonged capillary refill time, and poor pulse oximetry waveform can all indicate shock, even in the presence of a normal blood pressure.
- In addition to the history and physical exam, bedside ultrasonography and echocardiography can be an invaluable tool in phenotyping shock into hypovolemic, obstructive, distributive, and cardiogenic subtypes.
- Critically ill patients may have a dynamic illness course. Anchoring on the initial diagnoses can be mitigated through vigilance and frequent re-evaluations.
- Takotsubo cardiomyopathy is thought to be caused by severe catecholamine surges affecting the myocardium. Stressors resulting in catecholamine surges are abundant in the intensive care unit. Secondary Takotsubo syndrome is common, affecting up to 20% of ICU patients.

34.1 Introduction

Circulatory failure and shock is frequent in the intensive care unit, emergency department, and operating room. Shock is defined as acute circulatory failure with inadequate delivery of oxygen to the tissues. It can be subdivided into hypovolemic, obstructive, cardiogenic, and distributive subtypes. Hypotension often accompanies shock and in colloquial terms is often used interchangeably, although this is incorrect. Point-of-care echocardiography is increasingly used in the intensive care units to complement the physical exam and other monitoring modalities. Echocardiography can be used both as a hemodynamic monitoring tool with estimation of stroke volume and cardiac output and as a diagnostic tool used to phenotype the aforementioned categories of shock [1]. This evaluation should be ongoing to avoid erroneous treatment due to first impression bias.

Case Presentation

A 60-year-old woman presented to the emergency department in hemorrhagic shock due to hematemesis and melena. Her past medical history included chronic alcohol consumption and several previous admissions with alcohol withdrawal, orthopedic injuries after falls, and esophageal variceal bleeding. She had a 24-h history of vomiting and melena. She had a prehospital blood pressure of 73/55 mmHg and a pulse rate of 136. At admission, she was awake but confused. She was pale and diaphoretic with a barely palpable radial pulse. A radial arterial line was placed that revealed a blood pressure of 55/47 mmHg. Transfusions with packed red blood cells and plasma were immediately started.

On the initial arterial blood gas at admission, pH was 7.69 (7.35–7.45), pCO2 4.36 kPa (3.5–4.5), bicarbonate 40 mmol/L (22–29), pO2 8.8 kPa (11.1–14.4), potassium 2.1 mmol/L (3.5–5), sodium 142 mmol/L (136–146), ionized

calcium 0.99 mmol/L (1.15–1.29), lactate 6.2 mmol/L (0.7–1.6), and hemoglobin 11.6 g/dL (12–17.5). She received a potassium infusion, 1 g of tranexamic acid, pantoprazole 80 mg intravenously followed by a 8 mg/h infusion, and terlipressin 2 mg in case of variceal bleed.

She responded to blood transfusions to a stable systolic blood pressure of around 100 mmHg. Shortly after receiving calcium gluconate and terlipressin, the blood pressure rose and kept steady at around 140 systolic, potentially due to an inotropic response from calcium gluconate and a pressor response from terlipressin. Although the blood pressure stabilized, she remained in shock clinically with poor capillary refill time and paleness. Furthermore she had several bouts of emesis containing bright red blood in the emergency department. She was transferred to the operating room for an emergent upper endoscopy with ongoing fluid and blood products resuscitation in order to stop what we presumed was an ongoing upper gastrointestinal bleeding.

In the operating room, a quick risk/benefit analysis was performed whether to induce anesthesia and protect the airway with the risk for a potential for hemodynamic collapse on induction, or whether we should do light sedation to minimize the hemodynamic effects, but with the risk of airway compromise. As part of the hemodynamic risk assessment, we did point-of-care transthoracic echocardiography demonstrating a hyperdynamic heart with a small end-diastolic area and a small and collapsing inferior vena cava, consistent with hypovolemia. We continued transfusions and chose light sedation for the procedure using repeated doses of 5 mg esketamine and 2 mg midazolam. However, sedation was insufficient to provide optimal working conditions for the surgeon performing the endoscopy and she was intubated.

Upper endoscopy was performed demonstrating scant bleeding from a fibrotic area in the distal esophagus that was managed with adrenaline injections and subsequent placement of a temporary esophageal stent. Of note, varices were not seen. At this point in time the patient had received 3 units of packed red blood cells and 2 units of plasma. Anesthesia was maintained with an esketamine infusion of 2 mg/kg/h. She remained hypertensive throughout the procedure with systolic blood pressure in the 160–180 range, although with cool peripheries and a poor pulse oximetry waveform.

Since the bleeding had stopped and she was somewhat volume resuscitated, we opted to improve perfusion through vasodilatation. At first with incremental doses of fentanyl, up to a total dose of 0.5 mg and subsequently by switching esketamine to 1% sevoflurane. This markedly improved perfusion demonstrated through warm peripheries, good pulse oximetry waveform, and normalization of blood pressure until the clinical condition again deteriorated. The patient became pale, dusky, and gray in color, quickly followed by mottling on the extremities and truncus despite that the systolic blood pressure was stable (Fig. 34.1).

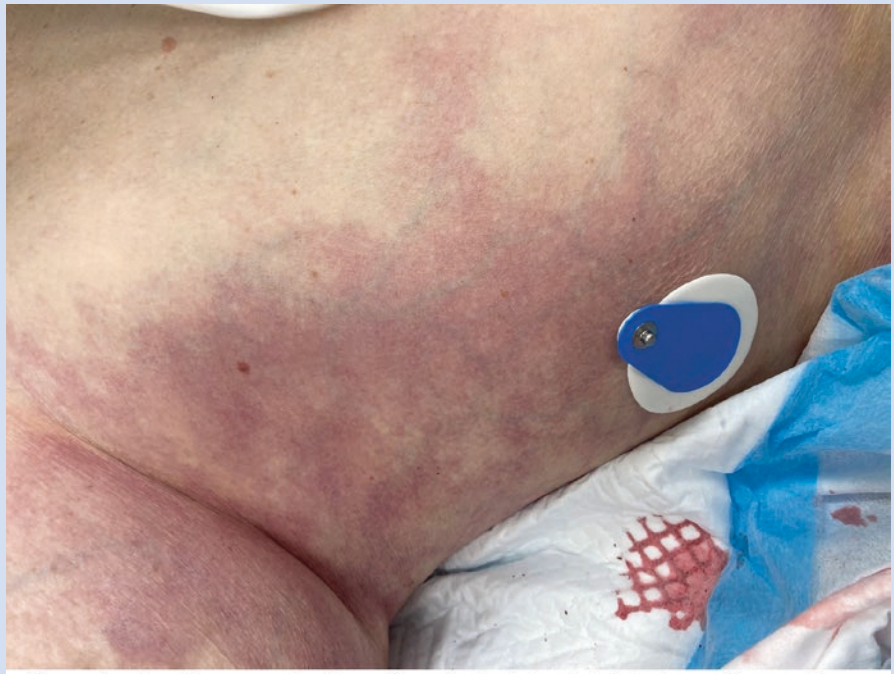

Fig. 34.1 Generalized mottling secondary to cardiogenic shock due to Takotsubo cardiomyopathy

34.2 Differential Diagnosis

Clinically the patient had returned to a shock state even more grave than on initial presentation, although the blood pressure remained normal. The patient had not received large amounts of blood transfusions, and re-bleeding with resulting hypovolemic shock was the primary suspected cause for persistent shock. However, the surgeon felt confident that the bleeding was controlled and the patient had stabilized on initial blood transfusions, both factors arguing against hypovolemic shock. The clinical findings were consistent with a poor cardiac output state making cardiogenic and obstructive shock a possibility but we did not feel the history of presenting illness strongly supported that diagnosis at that point in time. Distributive shock was felt unlikely given the history and clinical findings.

34.3 Investigations

A bedside echocardiogram was performed in order to phenotype the shock state. Surprisingly, the echocardiogram showed marked deterioration from the previous echocardiogram before induction of anesthesia. Left ventricular systolic function was severely depressed with an estimated ejection fraction of around 15%. There was

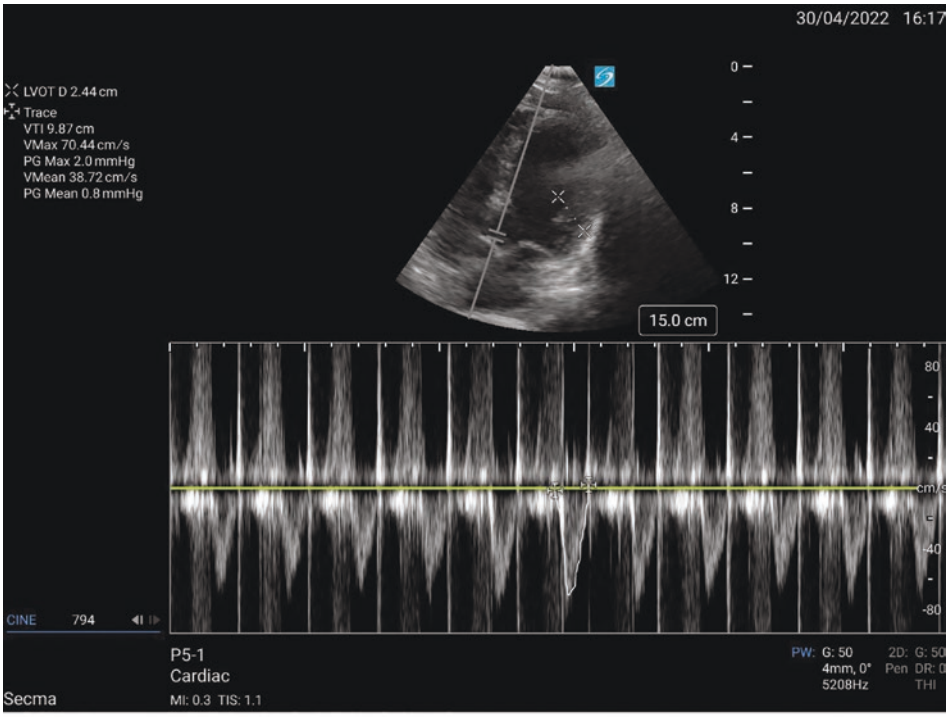

Fig. 34.2 Left ventricular outflow tract velocity time integral of 9.7 cm

evidence of mid ventricular hypokinesia and dilatation. The left ventricular outflow tract velocity time integral measured around 9 cm (18–22) consistent with a severely reduced stroke volume (Fig. 34.2). The inferior vena cava was dilated and without respiratory variation on positive pressure ventilation. Cardiogenic shock was diagnosed. A cardiology consultant interpreted the echocardiography and clinical findings as consistent with Takotsubo cardiomyopathy. On deeper scrutiny of the patient's medical chart it became apparent that the patient had Takotsubo cardiomyopathy 1 year prior secondary to alcohol withdrawal. She had at that time undergone coronary angiography excluding occlusive myocardial infarction. An electrocardiogram performed now on arrival at the intensive care unit showed no new findings and troponin T at arrival in intensive care was 28 nanograms per liter (<14) and pro brain natriuretic peptide was 1665 nanograms per liter (<287). Based on this information, the cardiology consultant decided that an emergency coronary angiogram was not indicated to exclude acute coronary syndrome.

34.4 Treatment

Inotropic support was initiated in the operating room with dobutamine at 5 mcg/kg/min and titrated until a maximal dose of 14 mcg/kg/min. She was transferred to the intensive care unit on mechanical ventilation. When sevoflurane was discontinued dur-

ing transport to the intensive care unit, the systolic blood pressure again rose to 180 mmHg. Sedation was continued with midazolam 4 mg/h and fentanyl 0.1 mg/h. Despite several sedation boluses, the blood pressure did not decrease and afterload reduction was commenced with a nitroglycerine infusion at 0.2 mcg/kg/min. Shortly after arrival in the intensive care unit, the mottling subsided, skin color improved, the extremities became warm, and the pulse oximetry waveform normalized. A repeat bedside echocardiogram showed some improvement in left ventricular systolic function. Left ventricular outflow tract velocity time integral had improved to 16 cm (18–22).

34.5 Evolution, Outcome, and Follow-Up

On the following day, the echocardiogram showed persistent severely reduced left ventricular function with affection of the entire apical two thirds of the ventricle. The right ventricle was not affected. No major valvular pathologies were seen. On day 2 the ejection fraction had improved to 40%. She remained sedated and intubated and was extubated on day 4. On the fifth day after admission, she was taken to the operating room and underwent anesthesia for removal of the esophageal stent. She was discharged home on the tenth day with ambulatory follow-up from addiction medicine services. On the day of discharge, the ejection fraction had improved to 58% and the left ventricular hypokinesis was no longer present.

34.6 Discussion

This case demonstrates the dynamic nature of critical illness and how a seemingly straightforward presentation such as hypovolemic shock in the setting of gastrointestinal bleeding can evolve into cardiogenic shock due to Takotsubo cardiomyopathy. It may be difficult to differentiate the different types of shock clinically. Point–of-care ultrasonography can be an invaluable tool in phenotyping shock. One such protocol is the RUSH protocol (Rapid Ultrasound for Shock and Hypotension) [2, 3].

In our case, both the clinical presentation and the initial echocardiogram were consistent with hypovolemia. On re-evaluation after the deterioration, echocardiography findings changed management dramatically. Had we anchored on the initial presumption of re-bleeding and continued volume replacement, we would certainly have worsened the patient's condition. Our rapid transthoracic echocardiogram performed at the patient bedside in the operating room helped make the diagnosis of cardiogenic shock. Instead of additional volume, we commenced inotropic support and afterload reduction, and the patient clinically improved.

The underlying etiology of cardiogenic shock in this case was Takotsubo cardiomyopathy. It is often referred to as "apical ballooning syndrome" due to the classical echocardiographic features of hypokinetic and akinetic mid- and apical left ventricle with a hypercontractile base. In this case, the patient had mostly mid-ventricular affection initially but the classical "picture" was seen the following day. Takotsubo cardiomyopathy is thought to be caused by excessive adrenergic stimuli which may paradoxically trigger cardiodepression. Beta 2 receptors are more abundant in the apical regions of the heart and may explain why this region is more commonly affected. Excessive catecholamine surges can be caused by physical, pharmacologi-

cal, and emotional stressors. Takotsubo may present as the primary problem. In the intensive care setting where underlying stressors due to critical illness are common, secondary Takotsubo syndrome may be seen in up to 20% of patients. Mortality is mainly caused by the underlying illness and co-morbid illness. The mainstay of treatment is supportive care [1, 4].

Finally, this case clearly demonstrates the fact that blood pressure does not equal flow. Even though the patient had a normal blood pressure, she had severely reduced cardiac output and end-organ perfusion. The importance of other clinical signs such as skin color, mottling, pulse oximetry waveform, and capillary refill time should not be disregarded despite a normal blood pressure.

Take-Home Messages

- Adequate blood pressure does not equal flow and end-organ perfusion. Clinical findings such as cold extremities, mottling, prolonged capillary refill time, and poor pulse oximetry waveform can all indicate shock, even in the presence of a normal blood pressure.
- Bedside point-of-care ultrasound and echocardiography can be an invaluable tool in differentiating and phenotyping shock into cardiogenic, obstructive, hypovolemic, and distributive subtypes.
- Secondary Takotsubo syndrome is common in the intensive care unit, affecting up to 20% of patients and should be on every intensivist's "radar" when evaluating patients in circulatory failure.

Summary

This is a case of a 60-year-old woman who presented in hypovolemic shock due to an upper gastrointestinal bleeding. She had a history of chronic alcohol abuse. Standard resuscitation measures with intravenous access and blood transfusions were started. She underwent an upper endoscopy in the operating room under general anesthesia. A bleeding fibrotic lesion in the distal esophagus was found and treated with adrenaline injections and placement of a temporary esophageal bleeding stent. After an initial stabilization she deteriorated in the operating room and developed severe circulatory failure. A point-of-care bedside echocardiogram was performed and demonstrated severely depressed left ventricular systolic function and mid-ventricular hypokinesia consistent with cardiogenic shock secondary to Takotsubo cardiomyopathy. Instead of further volume resuscitation, treatment efforts pivoted toward inotropic support and afterload reduction with dobutamine and nitroglycerine, respectively. She remained sedated, intubated, and ventilated in the intensive care unit for 4 days and gradually regained left ventricular function. On day 10 left ventricular hypokinesia had subsided and ejection fraction had improved from around 15 to 58%. The case demonstrates the usefulness of point-of-care echocardiography in phenotyping shock and how it can dramatically change management with improved patient outcome. Furthermore it demonstrates the importance of not relying on blood pressure as the sole measure of hemodynamic function.Acknowledgements Dr. Robert Pedersen for his kind teaching, inspiration, and mentoring. Dr. Thomas Lafrenz for supervision and support during the clinical management of the patient and during the case writing.

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Seizure-Associated Takotsubo Syndrome Complicated by Cardiogenic Shock and Successfully Treated with Levosimendan: A Case Report

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Contents

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Learning Objectives

- Takotsubo syndrome can be a cause of hemodynamic compromise following status epilepticus.
- Cardiogenic shock may be a life-threatening complication in the acute phase of Takotsubo syndrome.
- Levosimendan seems to have a beneficial role in the treatment of severe Takotsubo syndrome following status epilepticus.

35.1 Introduction

Takotsubo syndrome, a transient form of acute left ventricular dysfunction, has been increasingly reported, among other causes, in various central nervous system conditions, mainly traumatic brain injury, stroke, and subarachnoid hemorrhage [1, 2]. Seizure activity, and particularly status epilepticus, has less often been reported as a cause [3].

Although this entity is considered reversible, during its acute phase it may expose patients to life-threatening complications, such as cardiogenic shock and pulmonary edema. We report a case of Takotsubo syndrome subsequent to status epilepticus, complicated with cardiogenic shock, which was successfully treated with levosimendan.

Case Study

A 43-year-old woman was brought to the emergency department with generalized tonic-clonic seizures. Her medical history was remarkable for anorexia nervosa, alcohol abuse, and epilepsy for at least 8 years. A low compliance to antiepileptic therapy was reported. Diazepam and levetiracetam were administrated to control seizure activity; however, the patient did not regain consciousness. Her Glasgow coma scale score was 4/15; additionally, metabolic acidosis (pH = 7.1, lactate =14 mmol/L) was present. The patient was intubated for airway protection and mechanically ventilated and was transferred to our intensive care unit (ICU). She had no fever and a brain computed tomography scan was normal.

Upon ICU admission, the patient was hemodynamically stable, and her gas exchange had been normalized under mechanical ventilation. She was sedated with propofol; valproate was prescribed for seizure control. Shortly after admission, she developed hypotension requiring the use of noradrenaline infusion at a dose up to 2.1 μg/kg/min.

As part of routine diagnostic workup, an electrocardiogram (ECG) and a two-dimensional transthoracic echocardiography (TTE) examination were performed. The ECG showed sinus rhythm and was remarkable for ST depression up to 1 mm in leads V3–V6. The TTE revealed dyskinesia of all the basal segments of the left ventricle, with preserved contractility of the mid-cavity and apical segments. Left ventricular ejection fraction (LVEF) was calculated to be 35%. Moderate mitral regurgitation was also noted. All cardiac chambers were of normal dimensions, and the left ventricle was not hypertrophic. Troponin-T high sensitive levels were 380 pg/mL (reference limit<14 pg/mL). The diagnosis of Takotsubo syndrome was made, based on the typical findings of

regional wall motion patterns in the transthoracic echocardiography and electrocardiogram alterations. The differential diagnosis also included infectious myocarditis, coronary artery disease, and myocardial infarction in the absence of obstructive coronary artery disease as seen in Table 35.1.

Over the following 24 h, sedation was withdrawn and the patient was successfully extubated. However, due to persistent hypotension, noradrenaline at a dose of 1.2 μg/kg/min was continued. In addition, she had bouts of sinus tachycardia for which she was started on low doses of propranolol. The ST segment had become isoelectric but shown a slight flattening in leads V3–V6. Serial troponin level assessments had shown a trend to normalization. At this point, i.e., on the second day post-extubation, and still dependent on vasopressors, the patient developed acute pulmonary edema, which was treated with furosemide. An emergent TTE showed persistence of the previous findings. At this point the patient was offered coronary angiography, which she declined. There was an increasing need for vasopressor support associated with oliguria. She was subsequently started on a levosimendan infusion at a rate of 0.2 μg/kg/min, without a bolus dose. Forty-eight hours later, she was successfully weaned from the vasoactive medications.

A repeat TTE examination showed that contractility of the basal segment was markedly improved, the LVEF had increased to 45%, and the mitral regurgitation was significantly reduced. On the seventh day after ICU admission, the patient was discharged to the neurology department, and 2 days later, a fourth TTE was performed. The left ventricle was functionally normal, the LVEF was above 55%, and the mitral valve showed only trivial regurgitation. On the following day, the patient was discharged to home.

Table 35.1 Differential diagnosis

1. Infectious myocarditis; the patient had no clinical or laboratory evidence of infection
2. Coronary artery disease; coronary artery disease was less likely due to the typical for stress-induced cardiomyopathy echocardiographic findings; also, troponin levels were felt to be disproportionally low (the patient declined a coronary angiography)
3. Myocardial infarction in the absence of obstructive coronary artery disease (MINOCA); less likely to have ECG ST-segment alterations; also smaller degrees of troponin elevation than acute myocardial infarction with obstructive coronary artery disease (again, a coronary angiogram is required)

Discussion

Takotsubo syndrome represents a transient form of acute cardiac dysfunction without coronary artery involvement, known to accompany conditions that cause a catecholamine surge. Originally termed "Takotsubo cardiomyopathy" [1–3], it was thought to occur in post-menopausal women exposed to significant emotional stress. Similar descriptions of acute reversible left ventricular dysfunction, associated with electrocardiographic alterations and echocardiographic findings of ventricular wall dyskinesias, were subsequently made in a number of acute medical conditions such as hypoglycemia, pneumothorax, alcohol withdrawal, neuroleptic malignant syndrome, pheochromocytoma, sepsis, hemodialysis, and post anesthesia [1]. Several names have been given to this entity including the terms "broken heart syndrome," "apical ballooning syndrome," "stress cardiomyopathy," and "stress-induced cardiomyopathy" [1, 2]. In addition, atypical forms of Takotsubo syndrome, involving myocardial segments other than the apical region, are now well recognized. Also well-established is the fact that coronary lesions may coexist, usually in different territories than those exhibiting dyskinesia. The currently used 2018 InterTAK diagnostic criteria for Takotsubo syndrome [2] are summarized in ◘ Table 35.2.

The association of central nervous system conditions such as subarachnoid hemorrhage and traumatic brain injury with Takotsubo syndrome is well established in the literature [3]. Seizure activity and especially status epilepticus has also been associated with it, though rarely reported [3].

Initially, Takotsubo syndrome was considered to represent a benign and self-limited condition, considering the usual rapid recovery of LVEF within a few days. However, major clinical complications in the acute phase including cardiogenic shock

◘ **Table 35.2** 2018 InterTAK diagnostic criteria for Takotsubo syndrome. (Based on data from [2])

1. Transient LV dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical, midventricular, basal, or focal ballooning. RV involvement can be present. Transitions between types can exist. Wall motion abnormalities usually extend beyond the perfusion territory of a single epicardial coronary artery, but rare exceptions can exist (focal TS)
2. Emotional and/or physical triggers may precede onset of TS
3. Acute neurologic disorders or pheochromocytoma may serve as triggers for TS
4. New ECG abnormalities (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation). Rare cases without any ECG changes exist
5. Moderate elevation of troponin and creatine kinase and commonly significant elevation of BNP
6. Presence of CAD does not preclude a diagnosis of TS
7. Patients have no evidence of infectious myocarditis
8. Postmenopausal women are predominantly affected

Abbreviations: *CAD* coronary artery disease; *LV* left ventricular; *RV* right ventricular; *TS* Takotsubo syndrome; *CAD* coronary artery disease; *ECG* electrocardiogram; *BNP* brain natriuretic peptide

and pulmonary edema have been demonstrated in a subset of patients, ranging from 12 to 45% [1].

Given that a disproportionate catecholamine discharge is thought to be part of the pathophysiology of this entity, the use of catecholamines could worsen the cardiac stunning in such conditions. Alternative inotropic agents seem a reasonable choice, and one such agent, milrinone, has been successfully used in one reported case [4]. Levosimendan, a calcium sensitizer and ATP-sensitive potassium channel opener, had been proposed as early as 2007 for the treatment of Takotsubo syndrome [5]. In contrast to catecholamines, levosimendan enhances cardiac contractility without increasing myocardial oxygen demand. However, only a small number of neurologic patients presenting with cardiomyopathy has been treated with this agent [6, 7], and all of them had aneurysmal subarachnoid hemorrhage. To our knowledge, this is the first case of a patient with Takotsubo syndrome following status epilepticus, complicated with cardiogenic shock, which was successfully treated with levosimendan.

In conclusion, hemodynamic compromise following status epilepticus may be due to Takotsubo syndrome. In case it is complicated with cardiogenic shock, levosimendan may have a beneficial role in the treatment of this entity.

Take-Home Messages

- Cardiogenic shock may be a life-threatening complication of Takotsubo syndrome.
- Intensivists should be aware of Takotsubo syndrome in the differential diagnosis in patients presenting with status epilepticus along with hypotension.
- Several atypical variants of Takotsubo syndrome are now well described in the literature.
- Levosimendan may have a beneficial role in the treatment of severe Takotsubo syndrome following status epilepticus.

Summary

Multiple causes, including neurologic disorders, have been recognized as triggering factors of Takotsubo syndrome. However, association with status epilepticus has rarely been reported. We report a case of a 43 year-old woman who developed hemodynamic instability requiring vasopressor agents, after status epilepticus and need for mechanical ventilation. On ICU admission, the diagnosis of "typical" Takotsubo syndrome was made, based on typical findings of regional wall motion patterns in the transthoracic echocardiography, electrocardiogram alterations, and laboratory findings. On the following day, the patient was extubated, still dependent on vasopressors. However, over the following few hours she presented further hemodynamic compromise and developed cardiogenic shock and pulmonary edema treated with furosemide. Echocardiography showed persistence of the previous findings. Intravenous levosimendan treatment was initiated. Within the subsequent 2 days, the patient was progressively improved and weaned from the vasoactive agents. A repeat echocardiography examination showed marked improvement. She was discharged to the neurology department and subsequently to home with further echocardiography improvement. Given the

serious complication of cardiogenic shock during the acute phase of Takotsubo syndrome, and the reversibility of this entity, intensivists should be aware of Takotsubo syndrome in the differential diagnosis in patients with status epilepticus presenting with hemodynamic compromise, as well as of the treatment challenges.

Questions

- What is Takotsubo syndrome?
- Which conditions have been associated with TS?
- How is Takotsubo syndrome diagnosed?
- How is Takotsubo syndrome managed?

Answers

- Takotsubo syndrome is an acute reversible stress-induced cardiac event with characteristic transient left ventricular dysfunction that is triggered by emotional, physical, or combined events. It mimics myocardial infarction, but no angiographic evidence of obstructive coronary artery disease or acute plaque rupture is found, at least in typical forms (>80%).
- Both emotional and physical triggers such as sepsis, trauma, surgery, acute intracerebral conditions, respiratory distress, and recently, COVID-19 have all been associated with Takotsubo syndrome. However, some patients have no identifiable trigger.
- The diagnosis is based on the InterTAK criteria [2] (which represent a modified and more precise version of the revised Mayo Clinic Diagnostic Criteria). Echocardiography is of paramount importance. In several cases, the diagnosis can be established only with the use of cardiac magnetic resonance imaging. Final diagnosis requires recovery of Takotsubo syndrome-related wall motion abnormalities.
- Takotsubo syndrome is generally a transient disorder that is managed with supportive and symptomatic treatment. Control of the physical or emotional trigger event usually will result in resolution of symptoms. Some patients, however, develop acute complications such as shock and acute heart failure that require intensive therapy.

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Given the special role of catecholamines in pathogenesis of this entity, catecholamines and inotropes should be avoided. Levosimendan could be considered as a treatment option. Patients with persistent shock may need advanced treatment including continuous venovenous hemofiltration and veno-arterial extracorporeal membrane oxygenation.

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Cardiogenic Shock Due to Reversed Takotsubo Syndrome Associated with E-Cigarette or Vaping Product Use-Associated Lung Injury (EVALI): A Case Report

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Contents

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Learning Objectives

- Reversed Takotsubo syndrome may be associated to and complicate the clinical course of EVALI, which is a growing cause of acute respiratory failure and critical illness.
- Even though the relationship between these two clinical entities is still a matter of research, there are reports which point to a pathophysiological link. Both are diagnoses of exclusion and demand extensive investigation to be properly established.

36.1 Introduction

E-cigarette or vaping product use-associated lung injury (EVALI) is defined as respiratory failure with symptom onset within 90 days of the last reported use of electronic cigarettes with compatible radiologic findings, in the absence of other possible causes, especially infectious diseases; up to a third of patients may need endotracheal intubation and mechanical ventilation [1]. Takotsubo syndrome (TTS) is characterized by regional motion abnormalities in the left ventricle and can commonly result in acute heart failure and cardiogenic shock [2, 3].

Not only both entities are co-occurring in the same patient is a rare finding, they are both potentially an overlooked diagnosis in a critically ill patient with a not very clearly understood association.

Case Presentation

This is the case of a 30-year-old female who was admitted to the emergency room with symptoms of diarrhea, nausea, and vomiting, which started 48 h prior, that progressed into unproductive cough and dyspnea. Five hours after admission, she experienced an episode of syncope, with worsening hemodynamic status and acute respiratory failure. Vasopressor (norepinephrine) was promptly initiated, and the patient underwent endotracheal intubation and mechanical ventilation, with sequential admission to the intensive care unit (ICU). The patient was sedated with midazolam, through fentanyl neuromuscular blockade.

In her previous history, no recent flu-like symptoms were recorded, having received three shots of COVID-19 vaccines. A large consumption of alcohol and electronic cigarette use in the 48 h prior to the first symptoms have been reported. Based on her medical history, she had suffered a fracture in her left femur, 5 years ago, having undergone orthopedic surgery with placement of a hip prosthesis. No evidence of subsequent thromboembolic events was observed. No other prior conditions were reported.

36.2 Investigations

Initial tomographic assessment showed extensive and bilateral opacities with ground-glass attenuation, predominantly in the upper and middle lobes and in dependent regions, consistent with diffuse pulmonary edema or a nonspecific inflammatory pro-

cess. Laboratory tests initially indicated metabolic acidosis with increased anion gap, hyperlactatemia, and a PaO2/FiO2 ratio of 220. Bedside ultrasound was performed, showing significant left ventricular (LV) systolic dysfunction and inferior vena cava variability greater than 30%.

An electrocardiogram (EKG) study was also performed and showed sinus tachycardia, without suggestion of acute ischemia. Other laboratory findings demonstrated the following findings: ultrasensitive troponin, 496 ng/L; hemoglobin levels, 13.5 mg/dL; leukocytes, 7.400 per mL; neutrophils with immature cells, 16.100 per mL; and lymphocytes, 610. Other relevant findings were elevated C-reactive protein (CPR) levels and mild hyponatremia. Hepatic and renal function were preserved. An HIV test was performed, with a negative result.

Echocardiography showed significant impairment of LV systolic function, with an estimated ejection fraction (EF) of 20%. Due to the association of acute respiratory failure and cardiogenic shock, invasive monitoring using a pulmonary artery catheter was also performed to better assess hemodynamic parameters. Initial measurements showed normal right atrium and pulmonary artery systolic and diastolic pressures, with an increased pulmonary capillary occlusion pressure, reflecting a possible predominance of LV dysfunction. Central venous oxygen saturation was 75%. The patient had a CO2 gap of 3 mmHg, lactatemia of 4.5 mmol/L, and new troponin levels of 482 ng/L.

Toxicological tests showed negative results for multiple types of substances, and a viral panel including 24 pathogens using polymerase chain reaction method did not indicate viral presence in the collected samples. It should be noted that this panel included SARS-CoV-2 and influenza types A and B. Blood cultures, urine culture, sputum cultures, bronchoalveolar lavage, and tracheal aspirates also tested negative to the development of microorganisms. Autoimmune and rheumatological panels were also performed and demonstrated negative results.

Follow-up echocardiographic examination showed moderate impairment of global systolic function, relatively preserved in apical segments and markedly reduced in midbasal segments, with an EF of 35%. This pattern was suggestive of basal or reversed TTS, which was further corroborated by cardiac magnetic resonance. Moreover, spirometry examination was performed and did not indicate loss in pulmonary capacities or new pulmonary dysfunction.

36.3 Differential Diagnoses

Considering previous diagnostic workup and epidemiological history, a significant evidence for EVALI was found. Empirical antibiotic treatment was started using piperacillin-tazobactam and azithromycin, associated with methylprednisolone use. Based on previously reported tests, differential diagnoses with acute coronary syndrome (ACS), COVID-19, influenza, bacterial pneumonia, and pulmonary thromboembolism were excluded.

36.4 Treatment

Upon admission to the ICU, initial ventilator parameters were set in pressure-assisted mode, with protective ventilation parameters for acute respiratory distress syndrome. Nonetheless, hemodynamic status remained unstable, with doses of noradrenaline at 0.3 mcg/kg/min and a mean arterial pressure of 65 mmHg. Thus, volume replacement was initiated using 1000 milliliters of crystalloid solution. Despite initial measures, the patient required increasing doses of vasoactive drugs (VAD), specifically vasopressin. In the context of increasing doses of VAD and evidence of worsening of LV systolic function, dobutamine was started and titrated up to 10 mcg/kg/min.

36.5 Evolution, Outcome, and Follow-Up

After inotropes infusion was started, the patient demonstrated marked enhancement of ventricular function. The later improvement in LV function allowed for the gradual reduction of dobutamine and later of norepinephrine and vasopressin. Additional computed chest tomography and echocardiogram were performed. A marked reduction in bilateral superior and medial ground-glass infiltrate was observed, with new involvement of ground-glass areas suggestive of edema in both pulmonary bases, accompanied by moderate bilateral pleural effusion, whereas the echocardiographic study indicated a new estimated EF of 52%. A significant improvement in ventilatory parameters was observed, as shown by a PaO2/FiO2 ratio of circa 400 only 48 h after ICU admission. In view of hemodynamic and ventilatory amelioration, the patient underwent a spontaneous breathing test and was subsequently extubated. Significant improvement in hemodynamic and respiratory status allowed patient to be discharged from the ICU and be transferred to a nonintensive care unit. Workup at 96 h after admission demonstrated an EF of approximately 62%. Therefore, combined improvement and no worsening signs or symptoms allowed the patient to be discharged from the hospital on the sixth day after admission.

36.6 Discussion

This report has several strengths, which include the abundance of diagnostic tests and procedures performed, the absence of confounding factors, and its scientific novelty. While there is evidence that use of electronic cigarettes increases the risk of both myocardial infarction and stroke [4] and respiratory failure is known to precipitate typical TTS [5], the association between EVALI and atypical TTS is still rarely discussed, with only one abstract [6] available in the literature. Limitations of our case are those pertinent to all case reports, that is, being about a single patient and the inability to establish causality. The absence of similar case reports in our country, the exclusion of several other potential causes, and the existence of a physiological basis for the purported relationship are worth noting.

We present here; therefore, a case of EVALI in a young Brazilian patient, complicated by cardiogenic shock secondary to reversed or basal TTS. Physicians involved in the care of critically ill patients must keep this potential association in mind and

take the necessary steps to both establish it and discard the many differential diagnosis, as inadequate treatment during the acute phase of both diseases could result in catastrophic outcomes.

Take-Home Messages

- Adequate history taking is an essential part of the investigation of EVALI.
- Point-of-care ultrasound examination is extremely useful in investigating cases of shock of unknown etiology.
- There is evidence that EVALI may act as a trigger for cardiovascular and ischemic diseases.
- EVALI must be suspected as a cause of acute respiratory failure in patients with a compatible clinical picture.
- TTS and its variants must be suspected as potential causes of cardiogenic shock in patients with a compatible clinical picture.
- EVALI is increasingly reported as a trigger for reversed TTS.
- Management of both EVALI and TTS requires adequate exclusion of many potential differential diagnoses.
- The association of both entities may cause a fulminant disease, even if it may be self-limited.
- EVALI and TTS are entities that must be well understood by intensive care and emergency medicine practitioners.

Summary

This is the case of a 30-year-old woman with no prior chronic illnesses who presented with an acute case of gastrointestinal and respiratory symptoms, which rapidly progressed and required intensive care, mechanical ventilation, and vasoactive drug administration in elevated doses. Diagnostic and laboratory exams demonstrated significant impairment of LV function and troponin elevation; chest imaging was compatible with a diffuse inflammatory process. Workup did not reveal any bacterial or viral infectious diseases, rheumatological conditions, or coronary ischemia. Pulmonary artery catheterization was compatible with cardiogenic shock due to LV dysfunction. History of recent usage of electronic cigarettes coupled with echocardiographic evidence of basal abnormalities of LV function established the diagnosis of reversed TTS triggered by EVALI. Support treatment with antibiotics and corticosteroids was successful in weaning the patient from mechanical ventilation and allowing for asymptomatic hospital discharge with fully recovered pulmonary and LV function.

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Ivabradine as an Alternative to Beta-Blockade in Takotsubo Cardiomyopathy: Case Report

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Contents

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Learning Objectives

- Make a brief description of Takotsubo cardiomyopathy
- Present the clinical case of a patient with Takotsubo cardiomyopathy who presented as complications severe ventricular dysfunction with dynamic LV obstruction, QT prolongation, and intolerance to beta-blockers
- Describe the alternative management of heart rate control with ivabradine in a patient with intolerance to treatment with beta-blockers

37.1 Introduction

Takotsubo cardiomyopathy (TTC) is an increasingly recognized clinical syndrome characterized by reversible apical and mid left ventricular (LV) dysfunction mainly, in the absence of significant coronary artery disease. It was first reported in 1990 by Sato et al., who named the syndrome because the appearance of the left ventricle resembles a pot historically used in Japan to catch octopus [2]. TTC is more common in postmenopausal women. About 90% of patients are women with a mean age of 67–70 years and around 80% are older than 50 years [2, 3]. That is, it potentially triggered by emotional, physical stress, medical illness. The reason for the female predominance is unknown. Increased catecholamine surges have been proposed to play a central role in the pathogenesis of this condition [2]. The most frequent mechanisms are spasm of the epicardial coronary arteries, disorders of the microvascularization, and myocardial dysfunction. It is possible that endothelial dysfunction, which worsens after menopause, increases vulnerability to sympathetically mediated myocardial stunning.

Some patients present with an interventricular septum of sigmoid morphology, and an abnormal orientation at the insertion of the mitral valve, in the face of intense adrenergic stimulation or dehydration, would condition a reduction in ventricular volume and predispose to dynamic and transient obstruction of the LV outflow tract. This obstruction causes subendocardial ischemia secondary to reduced myocardial perfusion, which does not correspond to a specific territory of a coronary artery [2, 4, 5]. It is an entity clinically indistinguishable from acute coronary syndrome (ACS), the most common symptoms of TTC are acute chest pain, dyspnea, or syncope with enzymatic elevation of myocardial damage, anterolateral ST-segment elevation, and extensive anterior akinesia with LV apical bulging during angiography, but without significant alterations in the coronary arteries.

Coronary angiography with left ventriculography is considered the gold standard diagnostic tool to exclude or confirm TTC. The International Takotsubo Diagnostic Criteria (InterTAK) for the diagnosis of TTC and InterTAK Diagnostic Score may help improve the identification and stratification of TTC (Tables 37.1 and 37.2). Patients presenting with ST-segment elevation should undergo urgent coronary angiography (CAG) with left ventriculography to exclude acute myocardial infarction (AMI). In unstable patients, typical complications of TTC such as left ventricular outflow tract obstruction (LVOTO) should be determined with TTE and CAG to safely rule out AMI. In patients with normal coronaries on CCTA or CAG and typical ballooning patterns, cardiac magnetic resonance (CMR) should be performed to confirm the diagnosis [3].

Table 37.1 International Takotsubo Diagnostic Criteria (InterTAK Diagnostic Criteria)

1. Patients show transient left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery (focal TTC)
2. An emotional, physical, or combined trigger can precede the Takotsubo syndrome event, but this is not obligatory
3. Neurologic disorders (e.g., subarachnoid hemorrhage, stroke/transient ischemic attack, or seizures) as well as pheochromocytoma may serve as triggers for Takotsubo syndrome
4. New ECG abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes
5. Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common
6. Significant coronary artery disease is not a contradiction in Takotsubo syndrome
7. Patients have no evidence of infectious myocarditis
8. Postmenopausal women are predominantly affected

Table 37.2 InterTAK diagnostic score

InterTAK diagnostic score	
Female sex	25 points
Emotional stress	24 points
Physical stress	13 points
No ST-segment depression, except in lead aVR	12 points
Psychiatric disorders	11 points
Neurologic disorders	9 points
QTc prolongation	6 points
≤70 points low/intermediate probability of TTS	>70 points high probability of TTS

Acute complications occur in approximately 19% of patients, include tachyarrhythmias, bradyarrhythmias, pulmonary edema, cardiogenic shock, transient LV outflow tract obstruction, mitral valve dysfunction, acute thrombus formation, QT prolongation, stroke, and death. Hemodynamic and electrical instability during the acute phase expose patients to the risk of serious adverse in-hospital events require close monitoring and early intervention in unstable TTC patients. Moreover, it has been demonstrated that high heart rate and low systolic blood pressure are associated

with increased mortality in TTC. Ventricular arrhythmias, such as torsades de pointes, VT, or VF occur in 3.0–8.6%, are a frequent cause of death and occur most often in the subacute phase (hospital days 2–4) and coincide with anterolateral T-wave inversion and QTc prolongation [3].

Treat these patients with standard medications for LV systolic dysfunction with guideline-directed medical therapy for heart failure. Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) may potentially facilitate LV recovery. Diuretics are indicated in patients with pulmonary edema. Nitroglycerin is useful to reduce LV and RV filling pressures and afterload in the case of acute heart failure; however, the administration of nitroglycerin in the presence of LVOTO has been found to worsen. In the absence of HF, cautious administration of fluids and beta-blockers can be used to reduce hypercontractility of the LV base and thus increase cardiac filling and reducing obstruction. QTc prolonging drugs should be used cautiously in the acute phase because of the risk to induce torsades de pointes or VT and VF. Once the diagnosis has been done, acetylsalicylic acid can be discontinued unless there is concomitant coronary artery disease or peripheral vascular disease. Severe apical dysfunction makes thrombus formation likely. Heparin and warfarin are used to treat or prevent LV apical thrombi. Anticoagulants may be used if LV dysfunction is severe for several weeks, especially if recovery is slow. It is reasonable to continue anticoagulation until the LV function returns and thrombus resolution [1–3, 5]. In TTC patients with cardiogenic shock, those with apical ballooning should be promptly evaluated for the presence of LVOTO, which occurs in about 20% of cases. This should be performed during angiography with LV pressure recording during careful retraction of the pigtail catheter from the LV apex beyond the aortic valve. Similarly, a pressure gradient can be detected and quantified using Doppler echocardiography using continuous wave Doppler. Particularly, when using catecholamines, serial Doppler studies should be considered to detect an evolving pressure gradient. In patients treated with catecholamine drugs, a 20% mortality has been reported. Recently, it has been suggested that levosimendan could be used safely and effectively in TTC as an alternative inotrope to catechol amine agents. Furthermore, beta-blockers may improve LVOTO but are contraindicated in acute and severe heart failure with low LVEF, hypotension, and in those with bradycardia. Although evidence is unproven, TTC patients with LVOTO may benefit from the If channel inhibitor ivabradine [3].

Beta-blockers should be used cautiously, especially in patients with bradycardia and QTc >500 ms. As LV dysfunction and ECG abnormalities are reversible, an implantable cardioverter defibrillator for primary or secondary prevention is of uncertain value in TTC patients experiencing malignant ventricular arrhythmias [3]. Ivabradine decelerates the gradient of diastolic depolarization, causing a reduction of the intrinsic pacemaker activity in the sinoatrial node, and may be advantageous counteracting sinus tachycardia, possible modulating role in perivascular and interstitial inflammatory reactions in MI and acute myocarditis and acting as a vasodilator to abolish microvascular vasospasm. Ivabradine is a selective If channel blocker. It has not negative inotropic or lusitropic effects, reduces resting heart rate, and during exercise without affecting blood pressure. It provides a reduction of cardiac workload and energy consumption that may be beneficial in patients with ischemic heart disease, stable angina pectoris, and/or congestive heart failure. Furthermore, it has no negative dromotropic consequences, does not influence the QT interval, and

causes no coronary vasoconstriction. As it has been postulated that vasospasm is one of the pathogenic mechanisms of TTC, ivabradine may act as a vasodilator and/or spasmolytic [1]. Once the acute phase is over, the prognosis without significant comorbidity is good. Echocardiography 4–6 weeks after discharge is recommended to document normalization of ventricular function.

Patients who survive the initial event have a second event in approximately 5% of cases, mostly occurring 3 weeks to 3.8 years after the first event [2]. Typically, the LV function recovers and normalizes in few days to weeks.

Case Presentation

A 61-year-old woman, non-smoker, with a history of dyslipidemia and arterial hypertension treated with indapamide, no previous structural heart disease, no family history of cardiovascular disease, and without limitation for daily physical activity. Presented at home, being previously asymptomatic, sudden dyspnea, orthopnea, and expiratory wheezing. Her husband who is a nurse measures a SatO2 of 90% and brought her to the health center where she was diagnosed and treated as probable anxiety crisis and discharged home. The patient reported that she has had a few days with more physical activity and emotional stress since she has received a visit from her daughter and grandchildren, whom she had not seen for a long time. A few hours later, she deteriorated with worsening on breathing, oppressive chest pain without irradiation, and sweaty so she was referred to the emergency department. On arrival, she had baseline oxygen saturation of 85%, blood pressure of 111/74 mmHg, and heart rate of 110 bpm. On examination she presented tachypnea, expiratory wheezing, bilateral wet crackles up to the middle lung fields, no engorgement jugular vein, no murmurs, no hepatomegaly, no edema, and symmetric pulses in extremities. In the emergency department, oxygen therapy with 100% FiO2 was administered, and bronchodilators and systemic corticosteroids were administered thinking of the possibility of bronchospasm. After that, she didn't improve, and the chest pain persisted so admission to the ICU was decided. An electrocardiogram was performed again with pain, where sinus rhythm was observed at 82 bpm, normal axis, PR <200 ms, narrow QRS, QTc 546 ms, and 2 mm elevation in ST of V1-V2 with negative T of V3-V6 that was not present in ECG of emergencies (Fig. 37.1).

Laboratory results showed as relevant data hemoglobin 16.9 g/dL (12.0–17.0), hematocrit 48.6% (36.0–50.0), leukocytes 29.56 x10E3/μL, segmented 82% (40–75), lymphocytes 10% (19–48), platelets 320 x10E3/μL (140–400), prothrombin time 13.60 sec (12.00–16.00), prothrombin activity 100% (70–120), INR 1.00 (0.90–1.30), APTT 26.10 sec (23.00–36.00), D-dimers 0.210 μg/mL (0.300–0.500), glucose 247 mg/dL (75–110), sodium 140.3 mmol/L (135.0–145.0), potassium 3.3 mmol/L (3.5–5.1), creatinine 0.78 mg/dL (0.50–1.00), calcium 9.4 mg/dL (8.5–10.4), phosphorus 3.6 mg/dL (2.7–4.7), magnesium 2.0 mg/dL (1.7–2.8), C-reactive protein 0.23 mg/dL (0.00–0.80), and troponin T 187 pg/mL (<14 pg/mL), NT-ProBNP 2655 pg/mL (20–300). Given symptoms of acute coronary syndrome, we administer treatment with acetylsalicylic acid, clopidogrel, statin, and enoxaparin, and the patient was referred to hemodynamics in another hospital

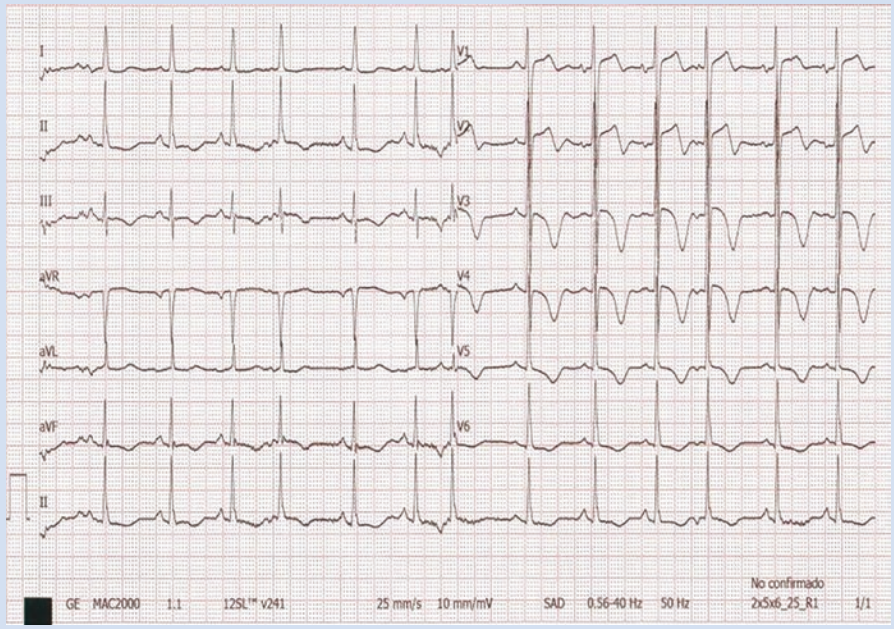

Fig. 37.1 Sinus rhythm at 82 bpm, normal axis, PR <200 ms, narrow QRS, QTc 546 ms, 2 mm ST elevation in V1-V2 with negative T in V3-V6

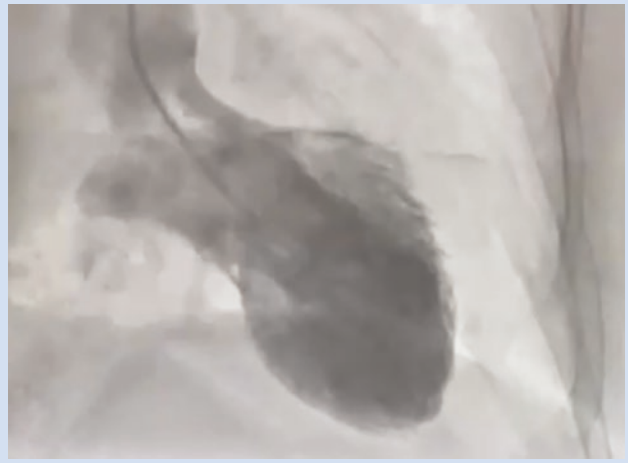

Fig. 37.2 Left ventriculography during coronary angiography in systole

where urgent coronary angiography was performed through the right radial artery, which showed the left common trunk, anterior descending artery, right coronary artery without lesions, and circumflex artery with non-significant proximal atheromatosis of 30% of obstruction. A ventriculography was performed that showed moderately dilated LV with anteroapical akinesia and hyperkinesia of basal segments (Fig. 37.2), globally ventricular dysfunction in the limit of

severity (angiographically 36.5%), and a LV-Ao gradient in withdrawal of 110 mmHg compatible with cardiomyopathy of Takotsubo. After the procedure, the patient was asymptomatic, was hemodynamically stable, and was returned to our intensive care unit.

37.2 Investigations

In the first 24 h of evolution, the patient presented hemodynamic worsening with arterial hypotension, tachycardia, orthopnea, bilateral crackles, radiographic worsening with bilateral infiltrates, oliguria, and metabolic acidosis with lactate of 4.5 mmol/L, clinically suggesting acute pulmonary edema with signs of congestion and cardiogenic shock. Semi-invasive hemodynamic monitoring was performed where it showed low cardiac output, low systemic vascular resistance, PPV, and SVV 13%, SvcO2 66%. It was decided starting hemodynamic support with norepinephrine up to 0.2 μm/kg/min and dobutamine up to 14 μg/kg/min, respiratory support with non-invasive mechanical ventilation (NIMV), diuretic treatment with furosemide, and echocardiogram was performed showing a dilated left atrium, LV with severe ventricular dysfunction with akinesia of the middle and apical segments, dynamic obstruction of the outflow tract with velocity of 5.5–6 m/s, normally functioning aortic valve, mitral valve with mild-moderate insufficiency with marked movement of the anterior mitral leaflet, no intraventricular thrombi are observed, non-dilated RV with preserved function. She continued requiring low dose of norepinephrine to maintain mean arterial pressure (MAP) but we discontinued dobutamine, so we decided to start for heart rate control ivabradine 5 mg every 12 h instead of beta-blockers due to the hemodynamic instability. Respiratory support and diuretic treatment were continued. In the following 48 h, she presented hemodynamic improvements with better heart rate control after starting ivabradine, allowing norepinephrine support to be lowered and for this reason IABP was not considered. After achieving negative fluid balance with furosemide, she presented respiratory improvement that allowed decreasing the oxygen therapy.

In addition, the patient presented acquired QTc prolongation up to 600 ms that normalized in the first week without presenting another arrhythmia. Within 10 days of evolution and after hemodynamic and clinical improvement, low-dose beta-blockade was introduced with good tolerance. On blood test the peak troponin T level was 550 pg/mL and NT-proBNP 28,000 pg/mL. Ultrasound controls were performed, showing improvement in ventricular function and a decrease in the gradient of dynamic LV obstruction. Ten days later, a severely dilated left atrium (AP 47 mm, volume 155 ml) was observed, non-dilated left ventricle (LVEDD 41 mm), moderate concentric hypertrophy (SIVd 14 mm), preserved LVEF (EF 56%), without alterations in segmental contractility, pseudonormal filling pattern E: 85 cm/s, A: 50 cm/s, E/A: 1.7, trivalve aortic valve with Vmax 1.6 m/s, mitral valve with very slight regurgitation, non-dilated RV, with preserved function (TAPSE 18 mm), slight tricuspid regurgitation that allows estimating a PSAP of 26 mmHg, and IVC not dilated.

During her admission, the patient presented fever and leukocytosis with normal procalcitonin; once receiving the results of serology of infectious diseases that were extracted as a differential study, she presented positive serology for phase II IgM antibodies of *Coxiella burnetii*, and treatment with doxycycline was started. In the anamnesis the patient denied having presented infectious symptoms prior to admission, no trips abroad, no contact with animals, or no consumption of unprocessed dairy products. Cardiac MRI was performed 11 days after admission, showing a non-dilated left ventricle, moderate hypertrophy of the basal posterior septum (14 mm) suggesting hypertensive heart disease, alterations of the mitral subvalvular apparatus and the mitral valve, acceleration in LVOT (left ventricular outflow tract) with SAM (systolic anterior motion) of mitral valve, hyperdynamic systolic function (LVEF 70%), right ventricle of normal size with preserved systolic function (RVEF 62%), edema in the mid and apical segments of the LV in the T2 sequences, and in late enhancement sequences, giving as a conclusion of the Takotsubo cardiomyopathy study with normal LVEF (70%); in addition, hypertrophy suggests hypertensive heart disease. It was recommended to repeat an imaging study in 3 years to rule out early-stage HCM given the alterations of the mitral subvalvular apparatus, and the dynamic gradient in LVOT due to SAM. Genetic study of hypertrophic cardiomyopathy was performed by massive parallel sequencing method using a library that included 18 genes related to hypertrophic cardiomyopathy (ACTC1, DES, FHL1, FHOD3, GLA, LAMP2, MYBPC3, MYH7, MYL2, MYL3, PRKAG2, PTPN11, TNNC1, TNNI3, TNNT2, TPM1, TRIM63, TTR), being a negative result with a sensitivity and specificity of the method higher than 99%.

37.3 Differential Diagnosis

Initially, the patient presented in the emergency department with data of acute ischemia in the electrocardiogram and elevated high-sensitivity troponin T; an urgent coronary angiography was performed to rule out ischemic heart disease due to coronary artery disease, which was ruled out. After performing the ventriculography, Takotsubo cardiomyopathy was diagnosed as the first possibility. A differential etiological study was performed, ruling out autoimmune, thyroid, or pharmacological pathology. In the study of possible infections, she only presented positive serology for IgM phase II antibodies to *Coxiella burnetii*, for which he received 20 days of treatment with doxycycline. After 3 weeks, the serology was repeated where the result was negative and during her follow-up, she did not present any data suggestive of clinical affectation, so she was discharged by the infectology team. Given that the cardiac MRI performed shows data of moderate septal hypertrophy with a slight dynamic gradient in LVOT due to SAM. It was recommended by cardiology to repeat the study in 3 years to rule out hypertrophic cardiomyopathy in an early stage. A genetic study of hypertrophic cardiomyopathy was also performed, which was negative. In addition, cardiac MRI confirmed the diagnosis of TTC and ruled out myocarditis.

37.4 Treatment

The patient was initially given medical treatment for ischemic heart disease with dual antiplatelet therapy with acetylsalicylic acid, clopidogrel, enoxaparin, and atorvastatin. After performing the coronary angiography and ruled out coronary artery disease, the treatment for ACS was discontinued. Progressively she presented clinical and hemodynamic worsening, she required respiratory support with NIMV and support with norepinephrine and dobutamine. Dobutamine was discontinued after a few hours since the echocardiogram revealed dynamic LVOT obstruction. Given the pulmonary congestion data, continuous furosemide infusion was administered and after achieving negative fluid balance, respiratory improvement was shown. On the first days, she presented sinus tachycardia, but given the hemodynamic instability, beta-blocker was not started, and it was decided as an alternative to control the heart rate, ivabradine. We had better control and maintained heart rates below 70 bpm. She was anticoagulated with LMWH (low molecular weight heparin) for the first week as prophylaxis for possible ventricular thrombus. She also presented an acquired prolonged QTc interval without another arrhythmia and progressively was correcting without any treatment. During the second week of evolution, the patient presented clinical and hemodynamic improvement, with very low oxygen requirements (2Lt), maintaining blood pressure without vasoactive agents and good urine output. Beta blocker and angiotensin-converting enzyme inhibitor were started at low doses with good tolerance, furosemide was maintained at a daily dose, and anticoagulation with LMWH was discontinued when she recovery normal ventricular function.

In this case, better control of heart rate and dyspnea was achieved after starting ivabradine; however, a causal relation between ivabradine and left ventricular recovery cannot be proven because the recovery of TTC-induced left ventricular dysfunction may occur spontaneously; however, ivabradine did improve the symptoms. Ivabradine is a selective If channel blocker. It has not negative inotropic or lusotropic effects, reduces resting heart rate and during exercise without affecting resting and exercise blood pressure. It provides a reduction of cardiac workload and energy consumption that may be beneficial in patients with ischemic heart disease, stable angina pectoris, or congestive heart failure. Furthermore, it has no negative dromotropic consequences, does not influence the QT interval, and causes no coronary vasoconstriction. As it has been postulated that vasospasm is one of the pathogenic mechanisms of Takotsubo cardiomyopathy, ivabradine may act as a vasodilator and/or spasmolytic [1].

37.5 Evolution, Outcome, and Follow-Up

In the first week the patient presented severe ventricular dysfunction with dynamic obstruction of LV, hypotension, and signs of cardiac congestion; she received treatment with norepinephrine and furosemide in continuous infusion; due to sinus tachycardia, prolonged QTc, and instability, beta-blockers were not administered in the acute phase. To control heart rate as an alternative, treatment with ivabradine was administered. Ivabradine is an If receptor blocker and decreases heart rate; it improves LV diastolic filling time and coronary perfusion as explained above. The

clinical and hemodynamic evolution of the patient was favorable and treatment with beta-blockade and low-dose ACE inhibitors could be introduced in the second week of evolution. Recovery of ventricular function and dynamic LV obstruction was confirmed by echocardiography and cardiac MRI, and other causes were ruled out. The patient is currently stable and is being followed up by the cardiology team.

37.6 Discussion

Takotsubo cardiomyopathy is a reversible cardiomyopathy characterized by left ventricular dysfunction and apical ballooning on imaging during systole. It predominantly occurs in post-menopausal women and is commonly associated with emotional or physical stress. Patients commonly present with chest pain like an acute coronary syndrome, but without angiographic evidence of obstructive coronary disease. The exact cause is unknown, but potential contributors include catecholamine excess and sympathetic nervous system hyperactivity [2, 6]. Left ventricular outflow tract obstruction, mitral regurgitation with or without anterior systolic motion, tricuspid regurgitation, arrhythmias, and QTc prolongation may also be seen [5]. The patient in our case presented severe ventricular dysfunction with dynamic LVOT obstruction and contraindication for starting beta-blockers in the acute phase due to acute cardiogenic pulmonary edema and hemodynamic instability. Ivabradine was administered to achieve better heart rate control with good results in the acute phase. When the patient presented clinical improvement and hemodynamic stability, beta-blockers were started with good clinical tolerance.

Ivabradine has been prescribed for the treatment of inappropriate sinus tachycardia, postural tachycardia syndrome, and TTC. A retrospective study reported symptomatic improvement in 60% of patients. Recently, it has been demonstrated in a single-center trial that ivabradine has improved the quality of life in patients undergoing coronary artery bypass grafting associated with conduction abnormalities or left ventricular dysfunction with relative or absolute contraindications to beta-blockers. In acute heart failure due to myocarditis, in a few cases, ivabradine was administered as an adjuvant off-label to patients with acute heart failure and multiorgan failure due to myocarditis; it has proven to be beneficial in supporting hemodynamic stabilization and showed a reduction of left ventricular mass index by significant heart rate reduction [1].

Although few cases have been described, Salah A.M. Said et al. [1] published the case of a 52-year-old female patient presented with TTC triggered by severe emotional stress and with symptomatic sinus tachycardia where, due to beta blocker intolerance, “off-label” treatment with ivabradine was initiated. Echocardiography revealed normalization of the ejection fraction at outpatient follow-up. There is no consensus on pharmacological treatment of TTC. Based on the suspected pathophysiology of the disease, adrenergic blockade using beta-blocker therapy is employed. Complete resolution of left ventricular wall motion dyskinesis occurs in the majority of TTC patients within days to weeks.

Take-Home Messages

- Takotsubo cardiomyopathy is commonly triggered by severe emotional or psychological stress and occurs primarily in postmenopausal women. High levels of catecholamines can temporarily stun the heart and produce the syndrome.
- Presents clinically as an acute coronary syndrome and is characterized by the absence of coronary lesions potentially responsible on coronary angiography.
- Coronary angiography with left ventriculography is considered the gold standard diagnostic tool to exclude or confirm TTC. The diagnosis is made based on the International Takotsubo Diagnostic Criteria (InterTAK).
- Produces a reversible contractility abnormality of the left ventricle that causes a balloon-like appearance that can be detected with echocardiography, during contraction of the ventricle; areas around the apex show a bottom-rounded hypokinetic apex with a narrow hypercontracted base.
- Acute complications include tachyarrhythmias, bradyarrhythmias, pulmonary edema, cardiogenic shock, transient LV outflow tract obstruction, mitral valve dysfunction, acute thrombus formation, QTc prolongation, stroke, and death.
- Treatment usually requires only supportive care in the acute stage because a reversal of the syndrome occurs in few days to weeks.
- Treating these patients with standard medications for LV systolic dysfunction with guideline-directed medical therapy for heart failure. These include angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics, particularly for volume overload states.
- Cardiogenic shock is managed with standard treatment. Inotropes are contraindicated in dynamic obstruction. Adrenergic agents are usually avoided to prevent further catecholaminergic stimulation.
- Beta-blockers may be limited by adverse reactions, intolerance, or contraindications. In case of beta-blocker intolerance, ivabradine, which reduces the heart rate and cardiac oxygen consumption, can be an option.

Summary

Takotsubo cardiomyopathy (TTC) causes a reversible left ventricle dysfunction that occurs mostly in postmenopausal women with or without cardiovascular disease that develops in the setting of acute severe emotional or physical stress. Approximately 2% of all patients with suspected acute coronary syndrome (ACS) have TTC. Within its etiopathogenesis, a decrease in blood flow has been evidenced in the apical and distal region of the septum; the most frequent mechanisms are spasm of the epicardial coronary arteries, disorders of the microvascularization, and myocardial dysfunction secondary to elevated levels of catecholamines, although the specific pathophysiology of this condition remains to be fully determined. Clinically mimics an ACS but without coronary lesions.

Coronary angiography with left ventriculography is considered the gold standard diagnostic tool to exclude or confirm TTC. The diagnosis is made bases on the International Takotsubo Diagnostic Criteria (InterTAK); echocardiography shows the left ventricle with hypokinesia or dyskinesia of the apical segments and hypercontractility of the basal segments.

The cardiovascular function returns to normal after a few weeks. Acute complications occur in approximately 19%, include tachyarrhythmias, bradyarrhythmias, pulmonary edema, cardiogenic shock, transient LV outflow tract obstruction, mitral valve dysfunction, QT prolongation, acute thrombus formation, stroke, and death. Initial treatment including angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors, diuretics, anticoagulation for prevention of thromboembolism, and beta-blockers that reduce heart rate are effective, but their use may be limited by adverse reactions, intolerance, or contraindications. In case of beta-blockers intolerance, ivabradine may act as a vasodilator, spasmolytic and reduces the heart rate and cardiac oxygen consumption so can be an option. We describe the case of a woman who presented with severe ventricular dysfunction with dynamic obstruction of LV, QTc prolongation, sinus tachycardia, and hemodynamic instability who did not tolerate beta-blockers and in whom ivabradine was administered for heart rate control with favorable evolution.

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Novel Immunotherapy and Mechanical Cardiac Support in Myocarditis: A Case Report

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Contents

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Learning Objectives

- To recognise the indications for mechanical circulatory support devices in myocarditis
- To understand the utility of endomyocardial biopsy and cardiac MRI in myocarditis
- The appreciate role of novel immunotherapies in myocarditis

38.1 Introduction

Myocarditis is an inflammatory disease affecting the heart. It may be infectious, autoimmune or idiopathic. Fulminant myocarditis (FM) is an uncommon yet life-threatening syndrome characterised by dysregulated immune response and acute-onset myocarditis associated with cardiogenic shock [1]. Important aspects of management include resuscitation and optimization of cardiac function, investigation of underlying aetiology and potentially immunosuppression.

This case report describes the use of veno-arterial extra-corporeal membrane oxygenation (VA-ECMO) for ventricular arrhythmias as a result of FM and demonstrates the use of endomyocardial biopsy (EMB) and cardiac MRI. We also describe the role of steroids and more novel immunotherapy, the interleukin-1 antagonist anakinra.

Case Presentation

GM was a 36-year-old man who presented to their local hospital with a 3 day history of abdominal pain, vomiting, lethargy and fevers. Associated symptoms included a poor appetite and nausea. He denied any chest pain.

He had no medical past history and was not on any regular medications. Working full-time as a barista, he was active and well prior to presentation. He smoked an average of three cigarettes a day, denied illicit drug use and exercised at the gym daily. Alcohol intake occurred on an occasional basis every 2–4 weeks. There was no significant family history and recent travel included a short trip to Denmark to visit family. He had received three COVID-19 vaccinations, the last of which was given 4 months prior to presentation.

On presentation to the emergency department, he was noted to be mottled and drowsy. On examination he was grey and ashen with a respiratory rate of 35 and a systolic blood pressure of 80 mmHg. He complained of epigastric tenderness on palpation, but his abdomen was otherwise soft on palpation with no guarding or signs of organomegaly. He had normal heart sounds with no audible murmurs and the central capillary refill time was 5 s. No added sounds were auscultated on chest examination.

An initial blood gas showed a lactate of 11.8 mmol/L. A central line was inserted and he was commenced on noradrenaline and then dobutamine. The decision was made to intubate him in the emergency department given his high oxygen requirements, as his oxygen

saturations were 90–95% on 15 L of oxygen via a non-rebreather. He was promptly intubated, after which his FiO2 requirement remained between 70 and 85%.

A point of care ultrasound showed severe left ventricular systolic dysfunction with no discernable regional wall abnormalities. There were no valvulopathies. A pulmonary artery catheter was placed which was unable to be wedged, but which showed a pulmonary artery pressure of 35/24 mmHg and a cardiac index of 1.6 L/min/kg^2.

Given his escalating vasoactive requirement and transthoracic echocardiogram (TTE) findings, he was discussed with our regional severe cardiorespiratory failure service for consideration of mechanical cardiac support (MCS). The initial advice was to review in 3 h to assess response to the current therapy. Two hours later, he was re-referred after developing new arrhythmias (Fig. 38.1), which oscillated between a right bundle branch block, left bundle branch block, first degree block and eventually episodes of non-sustained ventricular tachycardia, lasting 8–10 beats. They were associated with a static lactate and no interval change in the cardiac index.

On arrival of the retrieval team, the right bundle branch block and first degree atrio-ventricular block persisted, and episodes of non-sustained ventricular tachycardia were directly observed. The decision was made to initiate VA-ECMO given the high risk of a malignant arrhythmia leading to cardiac arrest. GM was subsequently cannulated percutaneously onto VA-ECMO and transferred to the retrieving ECMO-intensive care unit.

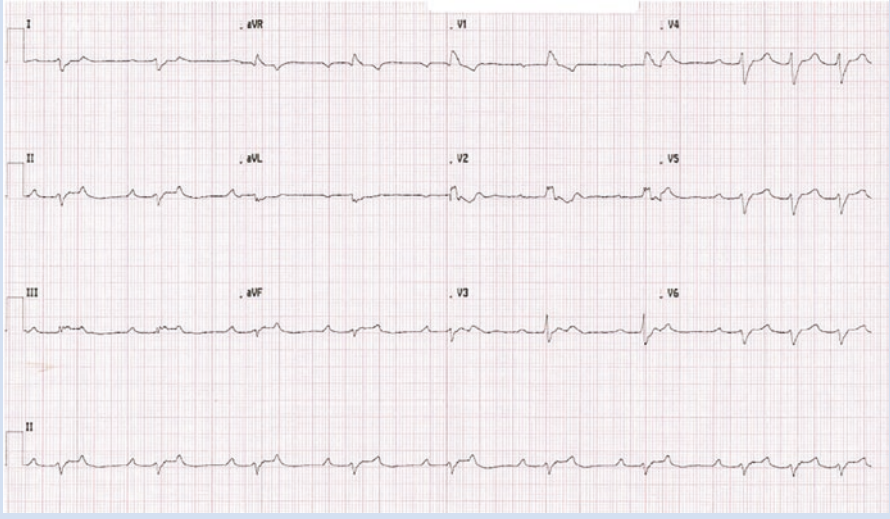

Fig. 38.1 Electrocardiogram

38.2 Investigations

GM's blood tests and other investigations were performed and in some cases repeated following retrieval. The results of his baseline pathology are shown in Table 38.1. They demonstrated a mild neutrophilia, KDIGO stage 3 acute kidney injury and an ischaemic hepatitis associated with a mild coagulopathy with prolonged INR. The initial ferritin was 85,590 μg/L, troponin was 16,018 ng/L, CRP 85 mg/L and procalcitonin was 6.18 μg/L. Cultures were sent from urine, blood and respiratory washings and failed to demonstrate significant growth. A COVID-19 screen was negative, as was an extended viral panel using PCR on respiratory secretions.

An auto-immune panel was performed which showed normal immunoglobulin A, G and M levels and was negative for anti-MPO antibodies, anti-PR3 antibodies, rheumatoid factor and ENA. Interleukin levels were measured (see Table 38.1) of which interleukin eight was particularly elevated.

Table 38.1 Baseline pathology

	Value	Reference range and units
Full blood examination		
White blood cell count	12.6	4–11 × 10^9
Haemoglobin	118	130–170 g/L
Platelets	96	150–400 × 10^9
Neutrophils	11.5	1.5–7.0 × 10^9
Lymphocytes	0.8	1.2–3.5 × 10^9
Monocytes	0.5	0.2–1.0
MCV	88	80–100 fL
Coagulation studies		
INR	1.8	0.8–1.2 ratio
Fibrinogen	3.1	1.7–3.9 g/L
Biochemistry		
Sodium	132	135–145 mmol/L
Potassium	5.4	3.5–5.0 mmol/L
Creatinine	347	59–104 μmol/L
Estimated GFR	17	70–130 mL/min
Ferritin	85,590	22–275 μg/L
Troponin	16,018	0–13 ng/L
Bilirubin	23	0–21 mmol/L
Alanine transaminase	>7000	4–59 IU/L

Table 38.1 (continued)

	Value	Reference range and units
Alkaline phosphatase	76	35–129 IU/L
Albumin	29	40–52 g/L
Creatinine kinase	1877	0–229 IU/L
LDH	6427	135–225 IU/L
Triglycerides	1.44	mmol/L
CRP	85	0–4 mg/L
Procalcitonin	6.18	0–0.05 μg/L
Immunology		
Interleukin 1b	<0.32	0 ng/L
Interleukin 6	27.10	0.76–6.38 ng/L
Interleukin 8	125.00	6.70–16.20 ng/L
Tissue necrosis factor alpha	25.8	7.78–12.2 ng/L
Interleukin 2 receptor alpha/CD25	7743	440–1435 ng/L
Interleukin 10	316	1.77–3.76 ng/L
Interleukin 17	<2.10	0 ng/L
Interferon gamma	0.44	0.54–2.72 ng/L

38.2.1 ECG

There was a variety of ECG changes observed over the first 24 h of admission (Fig. 38.1). The initial 12-lead ECG performed demonstrated a significantly prolonged PR interval and right bundle branch block. The PR interval worsened and at its longest measured 0.36 s. Other rhythms included a left posterior fascicular block and an intermittent left bundle branch block. No ST segment changes consistent with ischaemia were observed.

38.2.2 Imaging

The chest X-ray on presentation to the emergency department demonstrated prominent bilateral perihilar alveolar shadowing with upper lobe diversion.

A CT thorax, abdomen and pelvis with contrast, CT pulmonary angiogram and CT head were performed on return to our referral centre. In the thorax, there was predominantly central ground-glass opacification and intralobular septal thickening with right basal consolidation. There were shallow bilateral pleural effusions associ-

ated with compressive atelectasis, larger on the right. No pulmonary embolus or pericardial effusion was noted. Within the abdomen, there was normal appearance of all viscera and major mesenteric and portal vessels. The CT brain demonstrated no abnormalities and preserved grey-white differentiation.

A formal TTE demonstrated a non-dilated left ventricle, with moderately concentric thickening and severely impaired systolic function with an estimated ejection fraction of 20–25% and LVOT VTI of 12.9 cm. It was globally hypokinetic with no regional changes. Bands of echogenic material were noted within the left ventricular wall. The right ventricle was non-dilated with impaired longitudinal function (associated with a TAPSE of 11 mm) but preserved radial function. Bi-atrial size was normal, and no valvular pathology was noted. A trivial pericardial effusion measuring less than 0.5 cm was seen. The IVC was small and the return ECMO cannula was visualised.

38.2.3 Other Investigations

Twenty-four hours after retrieval, he underwent a bronchoscopy, which demonstrated a normal bronchial appearance with no secretions.

On day three of admission to the referral centre, GM underwent coronary angiography which demonstrated normal coronary arteries. An endomyocardial biopsy (EMB) was taken during this procedure. Four biopsies were sampled from the left ventricle, the largest measuring 3 × 3 × 1 mm. On microscopic examination, mild to moderate sub-endocardial and myocardial interstitial lymphohistiocytic inflammatory cell infiltrate was seen with occasional necrotic myocardial cells. There were no giant cells or granulomata, eosinophilia or plasma cell prominence.

38.3 Differential Diagnosis

The differential diagnoses considered were myocarditis (viral, autoimmune or infiltrative), giant cell myocarditis or haemophagocytic lymphohistiocytosis. An ischaemic cardiomyopathy was thought to be unlikely and was ruled out following a normal coronary angiogram. Following the cardiac biopsy results, the diagnosis of lymphohistiocytic myocarditis was made.

38.4 Treatment

38.4.1 Resuscitative and Supportive Therapy

GM was commenced on noradrenaline and dobutamine to support his haemodynamics. After developing arrhythmias, dobutamine was ceased and milrinone was commenced at a rate of 0.3 mcg/kg/min. He was given 50 mg of hydrocortisone and calcium chloride to aim for an ionised calcium above 1.2.

The cannulating team inserted catheters for VA-ECMO at the presenting hospital under fluoroscopy. The initial blood flows were 3.3–3.5 L/min and weaned down to

3.1 L/min by time of decannulation whilst sweep gas flows didn't rise above 2.0 L/min. He was anticoagulated with systemic heparin, titrated to achieve an anti-Xa of 0.3–0.5 IU/mL. A near-infrared spectrometer was applied to assess limb and cerebral perfusion.

Whilst noradrenaline weaned off quickly after starting VA-ECMO, milrinone was continued at 0.3 mcg/kg/min, ceasing on day four of admission.

Ventilation continued using a pressure support mode, with a positive end-expiratory pressure set at 12. Sedation and analgesia were provided in propofol and fentanyl infusions. Nasogastric feeds, multivitamins and thiamine were administered to support his nutritional state.

The creatinine rise noted on admission was associated with anuria. Renal replacement therapy was started shortly after retrieval utilising a CVVHD mode at a dose of 38 mL/kg/h.

Empiric antibiotics were commenced given the high inflammatory markers and uncertain aetiology. Piperacillin-tazobactam, amikacin and clarithromycin were given at the presenting hospital, which were changed to co-amoxiclav on retrieval. This was continued for 5 days until all results from blood, urine and broncho-alveolar lavage cultures failed to show significant growth of any organism.

38.4.2 Immunomodulation

A pulse dose of intravenous methylprednisolone (1 g daily) was started on presentation and continued for 3 days. The dose was reduced to 100 mg bd for 4 days and then down to 100 mg daily for 5 days. At this point oral prednisolone was started at 40 mg daily with a taper down of 5 mg every 3 days until cessation.

Anakinra, an interleukin-1 receptor antagonist, was started shortly after retrieval. The initial dose of 200 mg twice a day was given for 8 days and then reduced to 100 mg a day for a further 2 days before stopping.

38.5 Evolution, Outcome, and Follow-Up

The evolution of GM's disease was monitored by both imaging and biochemistry. Serial measurements of ferritin were performed to track the level of inflammation and showed a rapid descent from 85,590 down to 3088 in 7 days.

Serial TTEs were also conducted every 2–3 days. The first weaning study for VA-ECMO was done on day 3 of ECMO admission. On an extra-corporeal blood flow of 1 L, it showed a VTI of 11–13. A second weaning study on the fifth day of ECMO admission showed further improvement as the VTI increased to 16.9. This was associated with a cardiac output of 7.1 L/min and a visually estimated ejection fraction of 45–50%.

From a rhythm perspective, the dysrhythmias ceased by day 2 of ECMO admission, defervescing into a sinus rhythm with regular conduction intervals. Given the improving ejection fraction, declining ferritin and lack of further rhythm disorders, he was decannulated from VA-ECMO on day 5 of ECMO admission, undergoing surgical removal of catheters and embolectomy by the vascular surgery team.

GM was extubated the following day. Renal replacement therapy continued for another 4 days before ceasing. His creatinine continued to slowly improve, and he had no further need for renal replacement therapy after this time.

Six days after decannulation from ECMO, he was discharged to the cardiology ward. Here it was noted that he had an intermittent first-degree heart block. Two episodes of non-sustained ventricular tachycardia lasting 5–6 beats were also observed. A cardiac MRI demonstrated no active oedema but showed some subendocardial scar mid-septum which may account for the ongoing dysrhythmias. He was commenced on low dose beta-blockers and had no further ventricular tachycardia. Four weeks after initial admission and extensive physical rehabilitation, he was discharged home with a plan for outpatient cardiology follow-up.

38.6 Discussion

Lymphocytic myocarditis is the most prevalent form of myocarditis. Commonly associated with a viral precipitant, it may also occur in the absence of infection and in this setting is likened to other causes of inflammatory cardiomyopathy such as giant cell myocarditis and cardiac sarcoidosis [2]. In acute-onset viral myocarditis, it remains unclear what proportion of disease progression can be attributed to direct viral inclusions versus viral mimicry, dysregulated immune response and myocardial inflammation. Common symptoms on presentation include dyspnoea, chest pain and arrhythmias [3]. Atrioventricular blocks and ventricular arrhythmias are uncommon in FM, with the latter most commonly reported in those with giant cell myocarditis and cardiac sarcoidosis [2].

An early EMB helped to provide diagnostic clarity and guided the use of immunosuppression. It is the investigation of choice in those presenting with FM [1]. The risks of the procedure are higher in those requiring VA-ECMO but offset by the diagnostic yield [4]. Cardiac MRI has emerged as a non-invasive investigation in myocarditis. It has little role in the acute phase of fulminant myocarditis but may be useful in directing ongoing management by assessing patterns and progression of disease as well as the extent of focal fibrosis [2]. In less severe cases, it may be used to diagnose and characterise the pattern of inflammation. In GM, MRI differentiated between inflammation and fibrosis as the cause for his ongoing arrhythmias, aiding in the decision to continue weaning rather than escalate his immunosuppression.

Although GM had severe biventricular systolic dysfunction and worsening tissue hypoperfusion (INTERMACS 2), the primary role of MCS, at the point of cannulation, was to provide protection against progressive life-threatening arrhythmias. The choice of MCS depends on availability and the involvement of the left, right or both ventricles. It may consist of VA-ECMO, intra-aortic balloon pump, Impella/pVADs or a combination of these. Whilst cardiac failure and extracorporeal cardiopulmonary resuscitation are the most common indications for the use of VA-ECMO in FM, its use in dysrhythmias allows support of the circulation whilst minimising the risk of further arrhythmias associated with inotropes. Early commencement allows a period of stability during which investigations and targeted therapy can be commenced, prevents deterioration to the point of cardiac arrest, preserves end organ perfusion and is associated with improved survival [5].

Whilst steroids remain the backbone of immunosuppression for FM, the use of other immunotherapies is growing. Anakinra is an interleukin 1a and 1b receptor antagonist. It has been described in two previous case reports of myocarditis and is the subject of a current randomised control trial [6]. Interleukin levels do not predict response to therapy. In this case, its use was associated with a rapid improvement in inflammatory markers, left ventricular function and frequency of arrhythmias.

Take-Home Messages

- VA-ECMO should be considered for patients with myocarditis who experience life-threatening dysrhythmias and minimises the risk of inotrope-associated complications.
- Endomyocardial biopsy can provide early diagnostic clarity, whilst cardiac MRI has a useful role in the ongoing management of those with fulminant myocarditis.
- Immunosuppression is a key element in the treatment of fulminant myocarditis.

Summary

This case demonstrates that the use of early and advanced therapies is key in achieving an excellent outcome in fulminant myocarditis. VA-ECMO has an important role in supporting cardiac failure as well as in the prevention of inotrope-induced arrhythmias, particularly when dysrhythmias have already developed. Investigations have varying roles in the different phases of disease. Early EMB is gold standard and its use helps to guide therapy. Cardiac MRI has an emerging role within the recovery rather than acute phase of FM. Finally, a personalised approach to multi-modal immunotherapy and consideration of novel agents like anakinra are key in the rapid resolution of this life-threatening disease.

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Peripartum Cardiomyopathy: Diagnostic and Therapeutic Challenge

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Contents

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Learning Objectives

- Peripartum cardiomyopathy is a potentially life-threatening pregnancy-associated cardiac complication capable of progressing to acute heart failure with irreversible cardiac dysfunction.
- Confirmation of diagnosis of peripartum cardiomyopathy is primarily accomplished by echocardiography.
- Regardless of the sparsity of the condition, every intensivist should include peripartum cardiomyopathy in his or her differential diagnostic considerations when the corresponding findings occur to ensure adequate perioperative and intensive care management.
- Whenever this clinical pattern occurs, a thorough exchange of information between the various disciplines of cardiology, cardiac surgery, obstetrics, neonatology, anesthesiology, and intensive care medicine is required.

39.1 Introduction

Peripartum emergencies requiring intensive medical care constitute a serious challenge to the interdisciplinary treatment team. Owing to peripartum physiological alterations, symptoms may be masked and initiation of therapy may be delayed. Peripartum cardiomyopathy (PPCM) is a rare maternal cardiac complication characterized by acute restriction of mainly left ventricular cardiac function with typical signs of acute heart failure. In terms of clinical appearance, histomorphology, and therapeutic strategy, this etiologically incompletely characterized condition corresponds to dilated cardiomyopathy and is linked to late pregnancy and the first 5 months post partum. The extent a PPCM unmasks a clinically inapparent heart failure brought to light by the hemodynamic stress of pregnancy and puerperium or represents a distinct clinical entity is ambiguous to date. After idiopathic cardiac failure in the puerperium was first described in the nineteenth century, the term PPCM was precisely defined in the early 1970s [1]. Clinical symptoms are consistent with idiopathic cardiomyopathy. Although clearly formulated criteria should allow accurate diagnosis of this condition, it must be assumed that this cardiac phenomenon frequently is recognized at a very late stage or not at all in perinatal medicine. This results from the rarity of PPCM and the fact that apparently there is still a "perception weakness" for this diagnosis in clinical practice. For the above reasons and given a probable failure to diagnose mild clinical courses as PPCM, data on the incidence vary widely. Realistic figures place the incidence of PPCM up to 1:15,000 births with a clustering in hypertensive pregnancy, multiparous women, multiple pregnancies, and pregnant women over 30 years of age especially varying by geographic area [1]. Alcohol abuse, malnutrition, and association with the Negroid racial group have been discussed as other factors associated with PPCM frequency [1]. Diagnosis is primarily based on echocardiography, which reveals a marked diminution in systolic left ventricular function. Its therapeutic approach is likewise guided by the recommendations of idiopathic cardiomyopathies. This ranges from pharmaceutical approaches and mechanical cardiac support systems to a necessary heart transplantation as the last resort. The need to focus clinical attention on PPCM despite its low incidence arises from its high maternal mortality of 25–50% [1]. Thus,

close collaboration among the disciplines of cardiology, cardiac surgery, neonatology, obstetrics, and anesthesiology is essential. Intensive care management is focused on the unstable hemodynamic state of and on planning and performing perioperative management. Regardless of the sparsity of the condition, every intensivist should include peripartum cardiomyopathy in his or her differential diagnostic considerations when the corresponding findings occur to ensure adequate perioperative and intensive care management. On the basis of the presented case, the problem of PPCM will be pointed out.

Case Presentation

This case report describes the intensive care management of a 23-year-old female patient without any pre-existing medical history who spontaneously gave birth to a son and was discharged on the same day after an initially complication-free delivery which was performed under peridural anesthesia. Four days after spontaneous parturition, the patient presented again after an acute pain event associated with postpartum bladder voiding dysfunction. There, she presented the clinical picture of a severe abdominal condition with suspicion of peripartal sepsis. After diagnostic workup and detection of free intra-abdominal fluid, emergency laparotomy was indicated. This revealed a perforation of the urinary bladder. During anesthesia induction, pulmonary aspiration accidentally occurred and the patient developed an acute respiratory distress syndrome (ARDS). Treatment including prone positioning for 3 days and anti-infective therapy was carried out. Under the above measures, the patient's condition ameliorated markedly. However, on the following day, a rapid deterioration of her clinical picture developed involving increasing catecholamine requirements, hyperkalemia, lactic acidosis, massive increase of cardiac and hepatic biomarkers, and multiple bradycardic and tachycardic cardiac arrhythmias. Myocardial infarction was expeditiously excluded. Despite a norepinephrine dose of 3 µg/kg/min, the patient ultimately established a mean arterial pressure of merely 40 mmHg and subsequently required cardiopulmonary resuscitation (CPR). Therefore, as ultima ratio, an extracorporeal life support (ECLS) was established. Until the ECLS was deployed, the patient underwent CPR for more than 90 min, during which she consistently showed asystole or electromechanical decoupling on the electrocardiogram (ECG). At intensive care unit (ICU) admission, in addition to emergency hemodynamic stabilization, a comprehensive examination of the patient was performed. Diagnostic tools included physical examination, targeted determination of biomarkers of various organs and organ systems, and multiple imaging modalities.

Cardiovascular System

Echocardiography revealed a severely impaired left ventricular function (Fig. 39.1). After counterbalancing the potentially adverse reversible determinants of circulatory depression, electrical activity on the ECG was detected for the first time 8 h after ICU admission. However, this did not initially result in electromechanical coupling with formation of cardiac function. At an inherent rhythm below 20 beats/min, a low-dose inotropic therapy with dobutamine was initiated. This resulted in a progressively

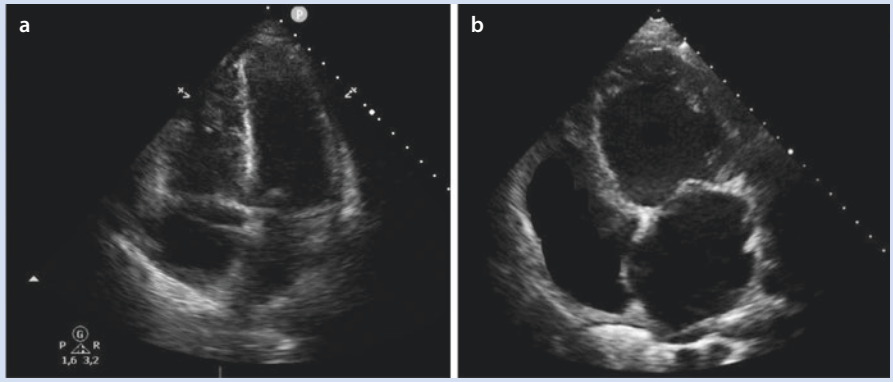

Fig. 39.1 Echocardiographic examination before and after admission to the ICU. **a** Preliminary echocardiographic examinations reveal inconspicuous left ventricular kinetics and LVEF. Interventricular septum (IVS) measures 10 mm, and right ventricular free wall measures 6 mm. **b** Subsequent evaluation under ECLS therapy displays severely reduced LVEF, and IVS is severely thickened measuring 16 mm, as is the right ventricular free wall measuring 12 mm. Thus, fulminant myocarditis is suspected. Because of a massive enlargement of the LV wall, there is a reasonable suspicion of giant cell myocarditis. Peripartum cardiomyopathy cannot be excluded by differential diagnosis. Likewise, septic myocarditis cannot be excluded. Given the acutely impaired hemostasis, a myocardial biopsy would be a high-risk procedure and should not be performed initially. Therapy for giant cell myocarditis would consist of the following: therapy of giant cell myocarditis with anti-CD3 antibody at 5 mg/day i.v. for 7 days (CAVE: initial hypotension), ciclosporin with target trough level of 100–120 µg/mL (contraindication to be checked beforehand! Control of liver and kidney values), methylprednisolone 1 mg/kgKG for 1 week, then reduction by 10 mg/4 weeks. However, since septic myocarditis could not be ruled out initially, only hydrocortisone was given and immunosuppressive therapy was not started yet. Since peripartum cardiomyopathy is also a differential diagnosis, additional ex juvantibus therapy with bromocriptine high dose is recommended (5 mg/day for 2 weeks, then 2.5 mg for 6 weeks)

increasing left ventricular ejection fraction. ECLS was weaned and terminated after 18 days following a prolonged course accompanied by frequent echocardiographic examinations. Initial echocardiographic examinations revealed a markedly enlarged myocardium of both the left and right ventricles, compatible with the appearance of myocarditis. Diagnostic testing for cardiotropic viruses remained without any pathologic findings. On completion of treatment, cardiac function presented with mildly reduced performance (LVEF 50%) and preserved right ventricular function. Given the exposure to a considerable extracorporeal circulatory surface, the patient developed an acquired von Willebrand's disease, necessitating VIII-VWF concentrate replacement therapy.

Renal System

In the presence of acute renal injury and pronounced metabolic acidosis, continuous venovenous hemodiafiltration (CVVHDF) was started immediately after acquisition (Table 39.1). This procedure was supplemented by hemoadsorption with CytoSorb® in the presence of massive hyperinflammation (interleukin-6 concentration >3000 pg/mL) and severe rhabdomyolysis with a peak myoglobin level of 59,242 ng/mL. Treatment was carried out in CVVHDF mode with

Table 39.1 Trend data of distinct biomarkers (acid-base analysis)

	Unit	Reference range	ICU admission	1 h	2 h	3 h	Day 2
paO_2	mmHg	70–105	480	255	244	152	156
$paCO_2$	mmHg	32–43	78	61	35	37	43
pH		7.37–7.45	6.92	7.04	7.30	7.37	7.43
Base excess	mmol/L	−2 to 3	−16.6	−13.6	−3.0	−5.3	2.2
BIC	mmol/L	21–26	11.8	13.8	22.0	20.0	26.3
Lactate level	mmol/L	0.5–1.6	12.7	11.9	9.3	7.8	4.5
Kalium	mmol/L	3.4–4.5	6.2	5.8	4.7	4.2	4.2
Glucose	mmol/L	3.9–5.8	4.0	3.3	3.4	3.4	7.6

citrate as anticoagulation at a blood flow rate of 100–150 mL/min. The combined application of both therapeutic procedures was associated with a resolution of metabolic acidosis. Hemodynamics stabilized and vasopressor support could be reduced and finally stopped during the treatment interval. Hyperinflammation could be rapidly controlled and all inflammatory parameters were reduced during the course of treatment (Table 39.2). Several cycles of citrate-CVVHDF, heparin-CVVHDF (due to metabolic alkalosis), and intermittent hemodiafiltration were performed. After 28 days, dialysis was successfully terminated as diuresis volumes as well as retention parameters progressively normalized.

Respiratory System

On admission, respiratory function was characterized by extremely limited lung compliance and pulmonary edema. Consequently, following a computed tomography (CT) scan, prone positioning was initiated (Fig. 39.2). Controlled ventilation using low tidal volumes could be re-established thereafter combined with fluid withdrawal. Combination of ECLS and prone positioning allowed pulmonary reconstitution, thus improving oxygenation and decarboxylation progressively. Recurrent pleural effusions were treated with chest tubes. In the absence of protective reflexes and delayed awakening, a dilatational tracheostomy was performed.

Gastrointestinal System

Acute liver failure required differentiated electrolyte and glucose replacement. Acute anemia with tarry stools manifested. Esophagogastroduodenoscopy revealed acute upper gastrointestinal hemorrhage with hemorrhagic gastritis. Hemostasis was reached by gastroscopical intervention. Because of rising laboratory signs of infection and an increase in abdominal circumference, a CT scan of the thorax and abdomen was performed for focus detection (Fig. 39.2). Here, conspicuous findings in the cavum uteri as well as a dilated cecum to transverse colon with locally reduced contrast of the

Table 39.2 Trend data of distinct biomarkers (organ-specific)

	Unit	Reference range	ICU admission	12 h	24 h	48 h	Day 8	Discharge
Hematocrit		0.35–0.47	0.23	0.21	0.25	0.23	0.24	0.22
Leukocyte count	10^9/L	4–9	16.1	11.1	25.7	18.7	22.4	14.3
Platelet count	10^9/L	150–450	21	47	42	32	78	359
Prothrombin time	%	70–130	15		24	34	74	91
INR		0.80–1.25	4.61		2.64	2.16	1.81	1.05
aPTT	sec	27–37	>250	72	56.9	49.9	50.2	29.3
IL-6	pg/mL		3046	2022		116		0.35
CRP	mg/L	<5	112				145	46.2
PCT	ng/mL	<0.064	1.18		3.22	3.77	5.53	0.18
ASAT (GOT)	U/L	<35	20,250		5648	3545	1453	145
ALAT (GPT)	U/L	<35	7721		1261	1274	679	101
Myoglobin	ng/mL	25–28	59,242	54,472	22,841	12,483	9591	
CK	U/L	<170	71,392		62,684	15,554	8117	
CK-MB	U/L	<24	1277		327	221	78.3	
Troponin-T	ng/L	<14	2389		1052	1173	838.0	
Creatinine	µmol/L	49–90	59		115	153	98.0	66.0
Urea	mmol/L	2.9–7.1	6.79		5.88	11.0	10.5	9.6
NH_3	mg/dL				99.9	69.1		
NSE	ng/mL	<16.3		121		154	78	

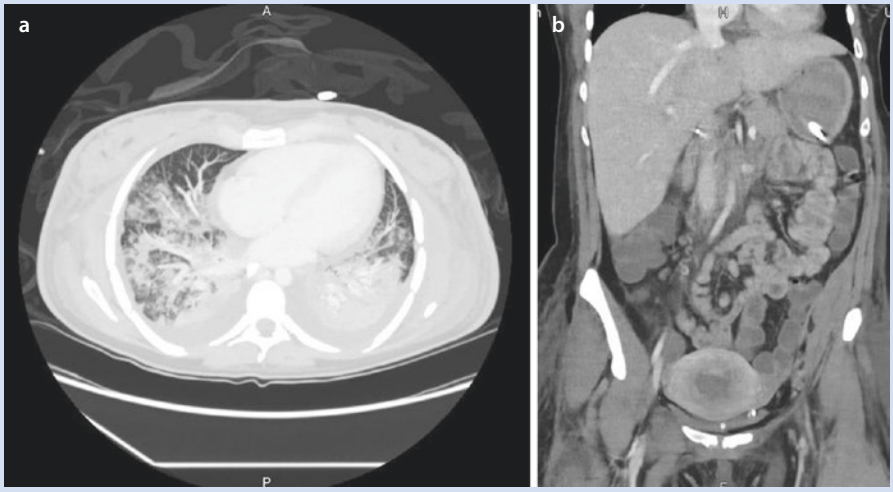

Fig. 39.2 Computed tomographic examination performed based on clinical deterioration. **a** Pleural effusions on both sides. Adjacent ventilation disturbances and additional consolidating infiltrates, more pronounced in the left lower lobe than on the right. Mottled lesions present in all lobes. **b** Suspicious uterus; dilated cecum to transverse colon with decreased contrast of the colon wall in some areas with suspected non-occlusive mesenterial ischemia

colon wall, possibly in the context of non-occlusive mesenteric ischemia, was revealed. Subsequent colonoscopy showed intestinal ischemia. With further rising laboratory and clinical signs of infection and catecholamine requirements, an emergency laparotomy was performed. The uterus was suspected as focus of infection; thus abdominal hysterectomy was performed. However, later histologic examination did not reveal any signs of inflammation.

Nervous System

Immediately before admission to the ICU, a cranial CT scan was performed (Fig. 39.3). During the course, repeated electroencephalographic examinations were performed. Together with multiple daily delirium screenings and extensive neurological examinations, she presented an encephalopathic pattern consistent with post-CPR status, albeit with substantial improvement over time. In the course of her complex and critical illness, the patient developed a severe intensive care unit-acquired weakness. Due to daily intensive physiotherapy, significant advances in locomotor function could already be achieved during the ICU stay and thus the patient could already be moved through the ward sitting upright before transfer to the rehabilitation facility.

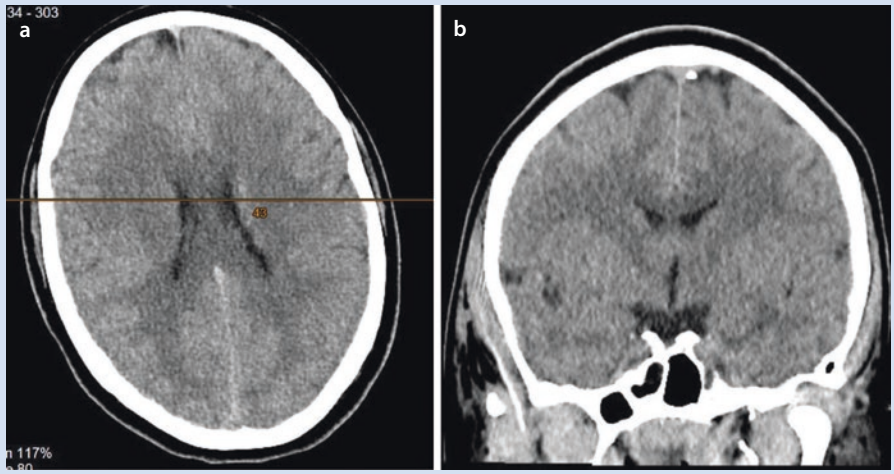

Fig. 39.3 Cranial computed tomography at ICU admission in two planes. **a** Axillary plane. **b** Coronary plane. Slender, medium-sized, and symmetrical ventricular system. Lean external cerebrospinal fluid spaces. No displacement of the interhemispheric gap. Regular cerebral sulcus relief on both sides. Medullary cortical differentiation preserved on all sides. Physiologic density of the basal ganglia, brainstem, and cerebellum. No evidence of intracranial hemorrhage, no infarct demarcation or early infarct signs

39.2 Investigations

In keeping with the clinical picture of PPCM, physical examination findings remain variable with limited specificity. Moist fine-bubble rales, leg edema, and a third heart sound may indicate a cardiac genesis of the symptoms. In many cases, however, there are no definite signs of heart failure on physical examination at initial presentation. Laboratory chemistry generally reveals a marked elevation of NT-proBNP. In contrast, other typical cardiac markers such as troponin or creatine kinase (CK) are not elevated or only slightly increased. CK as well as the inflammatory marker C-reactive protein (CRP) are also known to be elevated in the short-term postpartum, even in heart-healthy women [2].

The most important tool in diagnosing PPCM is transthoracic echocardiography given its widespread availability and noninvasive use. A normal echocardiogram excludes the diagnosis of PPCM. Typically, in PPCM, one finds a marked limitation of systolic left ventricular function; by definition, left ventricular ejection fraction is <45%, a condition often accompanied, but not always, by left ventricular dilatation, or dilatation of all 4 cardiac cavities (Fig. 39.1). Echocardiography to evaluate the right ventricle is also valuable in the diagnosis of pulmonary embolism, which is potentially coexistent or should be considered as a differential diagnosis. Furthermore, pathologies associated with echocardiography such as secondary mitral regurgitation, intracardiac thrombi, and pericardial effusions may be detected. Because of the

arbitrary repeatability of echocardiography, it should be applied particularly during follow-up assessment [1].

ECG, a continuously recorded measure, is part of standard monitoring and, in combination with clinical symptoms, may help to distinguish competing differential diagnoses (e.g., myocardial infarction, symptomatic cardiac arrhythmias, pulmonary embolism). In addition, it enables rapid and reliable detection of potentially occurring cardiac arrhythmias. Thus, a prompt treatment may be initiated. PPCM reveals no specific alterations in the ECG considered as "specific." However, inverted T waves indicating LV hypertrophy frequently appear. In addition, normal or "low-voltage" QRS complexes with inverted T waves or nonspecific ST-T wave changes may occur [1].

39.3 Differential Diagnosis

PPCM is a diagnosis of exclusion. Cardiomyopathies in pregnant women appearing prior to the last trimester usually arise from other origins, such as preexisting cardiac disease that decompensates under the increasing hemodynamic stress of advancing pregnancy. Congenital or acquired heart valve defects or preexisting asymptomatic cardiomyopathies often develop symptomatically during pregnancy. Hypertensive heart disease due to poorly controlled hypertension or gestational hypertension may also cause heart failure in pregnancy [1].

Peripartum myocardial infarctions are rare, but they are nevertheless frequently observed, especially in connection with the administration of oxytocin. It should be noted in particular that the peripartum period is associated with increased procoagulatory status, so that the risk of thromboembolic events is increased even in healthy parturients. Therefore, pulmonary embolism is often causative of dyspnea in the peripartum period and thus represents an important differential diagnosis. However, thromboembolic events also occur more frequently in the setting of PPCM because of the reduced cardiac output. Therefore, in the case of peripartum emboli, echocardiography should also be performed in any case to exclude right or left ventricular dysfunction. An echocardiographic examination should also be performed, if pneumonia is suspected during pregnancy or the puerperium, since supposedly clear signs of pneumonia such as cough, sputum, and dyspnea may also indicate heart failure due to PPCM [1].

Giant cell myocarditis is a rare, often rapidly progressive, and potentially fatal disease arising from T-cell lymphocyte-mediated inflammation of the myocardium typically affecting young and middle-aged adults. The disease course is often characterized by acute heart failure, cardiogenic shock, and ventricular arrhythmias. Diagnosis is often difficult because of the wide variety of clinical presentations and overlap with other cardiovascular diseases. Although cardiac biomarkers and multimodality imaging are often used as initial diagnostic tests, endomyocardial biopsy is required for definitive diagnosis. Immunosuppressive combination therapy, together with guideline-directed drug therapy, has led to a paradigm shift in the treatment of giant cell myocarditis, which is reflected in improved overall survival and transplant-free survival. Early diagnosis and prompt treatment may reduce the risk of transplantation or death, which remain common in patients with cardiogenic shock [3].

In the present case, further considerations regarding the causative triggers are of interest. The patient suffered from urinary retention after receiving an initially uneventful peridural anesthesia. Although extremely unlikely, a causative context cannot be ruled out completely. Furthermore, sepsis is of crucial importance in the peripartum period, because septic cardiomyopathy is a relevant differential diagnosis in addition to PPCM. Sepsis in the peripartum period is a life-threatening condition that accounts for 4.7% of maternal mortality in industrialized countries despite established screening. Worldwide, peripartum sepsis-associated mortality is 11%, making it one of the leading direct causes of gestational death [1].

Metabolic disorders potentially represent life-threatening situations. Besides the most common entities like diabetic metabolic derangements, the so-called Sheehan syndrome is of particular interest. It refers to postpartum hypopituitarism caused by ischemic necrosis due to blood loss and hypovolemia during and after delivery. The signs and symptoms of panhypopituitarism are diverse due to the involvement of various hormonal insufficiencies. The most common hormones lost are growth hormone, followed by gonadotropins, adrenocorticotropic hormone, and thyroid-stimulating hormone [4].

39.4 Treatment

Management of PPCM patients is based on the Guidelines for the Diagnosis and Management of Acute and Chronic Heart Failure published by the European Society of Cardiology. First and foremost, assessment of the patient's hemodynamic status and evaluation of the signs and symptoms of congestion and cardiogenic shock is crucial [1].

The case presented here relates primarily to the management of hemodynamically unstable acute PPCM. Women presenting with acute heart failure and cardiopulmonary stress (e.g., systolic blood pressure <90 mmHg, peripheral oxygen saturation <90%, or lactate >2.0 mmol/L) need to be immediately transferred to an intensive care unit based at an experienced center. Depending on volume status, it is necessary to optimize preload with either fluid supplementation or diuretics. If systolic blood pressure exceeds 110 mmHg, vasodilators are recommended to improve afterload (preferably hydralazine during pregnancy). If hemodynamic instability is present, inotropes and/or vasopressors may be required. Nevertheless, a point worth highlighting in this regard is the potential adverse effects of catecholamines (especially dobutamine) on PPCM patients, which ought to be shunned whenever possible. Administration of levosimendan appears to be safe and as such is preferable. Early evaluation of mechanical circulatory support is recommended. Various devices are available for this purpose. Percutaneous devices (such as the Impella® microaxial pump) are preferred in patients showing isolated left ventricular failure, whereas a combination of a percutaneous device and an ECLS is recommended in patients presenting biventricular failure. In addition, termination of pregnancy by urgent delivery via cesarean section is mandatory in prepartum cases. Corticosteroids for fetal lung maturation should be administered to women up to 34 weeks of gestation [1].

In PPCM patients whose hemodynamics remain stable without cardiopulmonary stress and who have an ongoing pregnancy, therapy should focus on optimizing maternal hemodynamics and careful fetal observation. Heart failure treatment is limited to beta-blockers, vasodilators (preferably hydralazine), and diuretics in case of fluid overload. In hemodynamically stable patients, vaginal delivery is the preferred method [1].

Treatment regimens for all patients should include bromocriptine. Bromocriptine treatment should always be accompanied by at least prophylactic anticoagulation to prevent thrombotic/thromboembolic events [1].

39.5 Evolution, Outcome, and Follow-Up

The patient was discharged from the intensive care unit after 47 days and transferred to a rehabilitation clinic. By the end of intensive care, cardiac function returned to baseline. Likewise, the integrity of all other organ systems recovered. Of particular importance to be emphasized is the neurological outcome achieved by the patient. Hence, a re-examination performed after 1 year of follow-up revealed a completely recovered young mother, who is entirely capable of fulfilling her everyday responsibilities.

39.6 Discussion

PPCM is a potentially life-threatening pregnancy-associated cardiac complication that can lead to acute heart failure with irreversible cardiac function. There are various case reports on this clinical condition. In general, pregnant patients before birth are concerned, who became conspicuous with clinically unspecific symptomatology. In these cases, the attentiveness of the physician and the inclusion of PPCM in the differential diagnostic considerations is of enormous importance. Indeed, this provides the basis for targeted diagnostics and, if necessary, the initiation of specific monitoring and therapeutic measures. Among other things, a rapid and controlled delivery is crucial not only to save the life of the mother but also that of the newborn. The case presented here is different because the patient had already given birth at the time of admission. The initial diagnostic workup underscores the critical situation and the resulting life-threatening nature of the case. Therefore, in consultation with the cardiac surgery department, implantation of a cardiac supporting system in the sense of veno-arterial extracorporeal membrane oxygenation was performed. Other systems such as intraaortic balloon pump, left ventricular assist device, or Impella® are also applicable depending on the impairment of cardiac function and the expertise of the medical team. All methods may be suitable as (temporary) therapeutic options in female patients. An assist device may be considered in PPCM both as a "bridging" method for a targeted heart transplant in the usually isolated cardiac disease and otherwise healthy patients, but may also find application as a final therapy to prolong life. Primarily, weaning from the implanted device should be pursued in terms of restoration of cardiac function. This was impressively achieved in the presented case. Other case descriptions showed similar courses: Emmert et al. described

a patient who continued to have cardiogenic shock after cardiac decompensation despite heart failure therapy and intra-aortic balloon pump implantation. As a result, the decision was made to implant an LVAD. Following conservative medical therapy, the assist device was finally explanted successfully after several months [5]. Furthermore, a case series showed that implantation of an ECLS in patients with peripartum cardiac dysfunction is a serious therapeutic option that should be integrated early in the decision-making process under strict risk-benefit considerations. However, serious incidence of complications associated with this therapeutic option remains a concern. Among others, thromboses as well as hemorrhages are possible due to the required anticoagulant therapy, which can be life-threatening for the patients [6].

In conclusion, rapid diagnostics, consistent initiation of therapeutic procedures at highest clinical and scientific level, and close interaction of the various medical specialties saved the patient's life and provided her with a serious opportunity to shape her future life in a self-determined fashion.

Take-Home Messages

- PPCM is a potentially life-threatening pregnancy-associated cardiac complication capable of progressing to acute heart failure with irreversible cardiac dysfunction.
- Confirmation of diagnosis of PPCM is primarily accomplished by echocardiography.
- Regardless of the sparsity of the condition, every intensivist should include peripartum cardiomyopathy in his or her differential diagnostic considerations when the corresponding findings occur to ensure adequate perioperative and intensive care management.
- Whenever this clinical pattern occurs, a thorough exchange of information between the various disciplines of cardiology, cardiac surgery, obstetrics, neonatology, anesthesiology, and intensive care medicine is required.
- If cardiogenic shock with refractory hypotension and cardiovascular failure occurs, implantation of cardiac assist devices may be indicated.
- Prognosis varies depending on the improvement of patients' heart failure within the first months postpartum.

Summary

Peripartum emergencies requiring intensive medical care impose a major challenge on the interdisciplinary treatment team. Due to physiological changes during the peripartum period, symptoms may be masked and initiation of therapy may be delayed.

This case report describes the intensive care management of a 23-year-old female patient with no previous medical history who spontaneously gave birth to a son after an initially complication-free delivery under peridural anesthesia. She was discharged from the hospital on the same day. Her readmission occurred 4 days after discharge due to abdominal pain. Following sepsis progression accompanied by ARDS, she initially achieved short-term stabilization with reconstitution of all organ systems. In the setting of acute cardiac decompensation, most consistent with peripartum cardiomyopathy, necessity emerged to implement an ECLS. Under targeted multimodal

therapy, continuous improvement of the patient's condition was achieved. As a result, she could be discharged to rehabilitation after 47 days without organ dysfunction and, most importantly, without neurological deficit.

Peripartum cardiomyopathy is a rare maternal cardiac complication characterized by acute restriction of mainly left ventricular cardiac function with typical signs of acute heart failure. However, with early diagnosis and adequate therapy, there is a chance of recovery. Patients should be evaluated by echocardiography. Because of the low incidence of PPCM, there is usually little or no experience in treatment, and established interdisciplinary collaboration in care is essential, PPCM patients should be treated at experienced major centers. Optimal therapeutic regimens include beta-blockers, ACE inhibitors, and MRA. In case of cardiogenic shock with refractory hypotension and cardiovascular failure, implantation of cardiac support systems (ECLS, ventricular assist devices) up to heart transplantation may be indicated. Depending on the improvement of the patients' heart failure within the first months postpartum, the prognosis also varies. However, the lethality of the clinical picture remains high.

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Impact of Perioperative Veno-arterial Extracorporeal Membrane Oxygenation on Outcome in a Patient with Impaired Cardiac Function Undergoing Open Thoracoabdominal Penetrating Aortic Ulcer Repair

Igor Abramovich, Ann-Kristin Adamsen, and Stefan Angermair

Contents

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Learning Objectives

- Readers will be able to illustrate various complications following open surgical repair and treatment of penetrating thoracoabdominal aortic ulcers.
- Readers will be able to describe how to support patients with heart failure during high-risk surgical procedures in intensive care units.
- Readers will be able to discuss potential benefits of perioperative veno-arterial extracorporeal membrane oxygenation.

40.1 Introduction

Despite procedural improvements in vascular surgery, anaesthesia, and intensive care, patients with thoracoabdominal aortic aneurysms still have a 30-day mortality rate of about 8% after surgical treatment, even when the procedures are performed in experienced centres [1]. Outcomes in patients presenting with isolated ruptured penetrating aortic ulcers have a similar mortality rate of up to 12% and a morbidity rate of 31%, respectively [2].

Although interventional procedures such as endovascular repair are currently available, the rate of associated postoperative complications remains significant with both procedures [3]. Specific complications include renal, pelvic and intestinal ischaemia, endovascular complications and cardiopulmonary failure. In addition, non-specific complications such as thromboembolic events, stroke and myocardial infarction may also occur.

To reduce complications after open aortic repair in patients with pre-existing heart disease and to prevent abdominal ischaemia (usually by cutting off from arterial blood supply for a limited time during aortic replacement surgery), several centres worldwide have started to use veno-arterial extracorporeal membrane oxygenation to support circulatory function.

Our case report demonstrates the appropriate use of veno-arterial extracorporeal membrane oxygenation in intensive care and cardiac optimization as well as the positive impact on patient outcomes.

Case Presentation

An 81-year-old man was admitted to our interdisciplinary surgical intensive care unit with abdominal pain that had persisted for 3 weeks. The physical examination and abdominal computed tomography indicated a ruptured penetrating aortic ulcer. There was a known pre-existing infrarenal abdominal aortic aneurysm of 4.8 cm in his medical history. His pre-existing conditions included coronary artery disease, type II diabetes mellitus, atrial fibrillation, dilated cardiomyopathy with chronic heart failure with a reduced ejection fraction of 35% supported by a pacemaker and an implantable cardioverter-defibrillator, chronic renal failure and resuscitation after allergic shock without neurological impairment.

40.2 Investigations

In the physical examination, the patient was awake and conscious and described severe acute abdominal pain associated with hypertensive blood pressure.

A computed tomographic angiography was performed which showed a penetrating aortic ulcer of the superior mesenteric artery and a progression of the known infrarenal abdominal aortic aneurysm of 5.8 cm (which was previously known to be 4.8 cm), associated with a stenosis of the celiac trunk and dilatation of both iliac arteries (Fig. 40.1). A transthoracic echocardiography confirmed pre-existing heart failure with a reduced ejection fraction of about 35% without relevant valve defects.

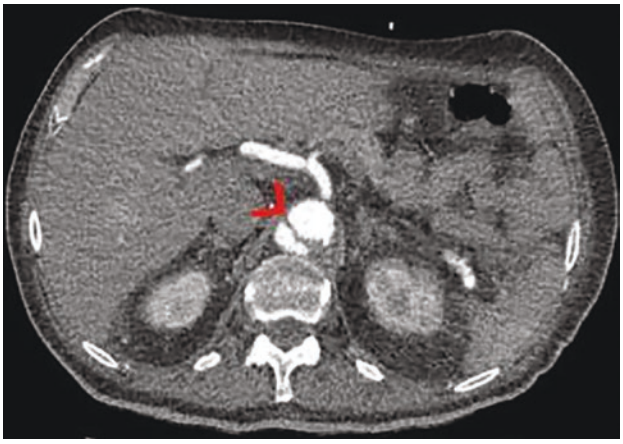

Fig. 40.1 A computed tomographic angiography showing a dorsally covered ruptured penetrating aortic ulcer of the abdominal aorta at the level of the superior mesenteric artery

40.3 Differential Diagnosis

Possible diagnoses were associated with various genetic disorders, such as Marfan syndrome, Ehlers-Danlos syndrome and Dietz syndrome. Considering the patient's pre-existing condition and the age, these diagnoses were considered highly unlikely.

Other infectious diseases, such as aortitis syphilitica, were excluded, as there was no relevant history or evidence of relevant infections.

Autoimmune vasculitis, such as giant cell arteritis and Takayasu's arteritis, were considered unlikely because of the absence of inflammatory parameters.

40.4 Treatment

After admission to our intensive care unit, the patient's blood pressure was normalized by intermittent intravenous administration of urapidil, which was adjusted to his existing hypertension medication to keep systolic pressure under 120 mmHg and control the symptoms of the ruptured penetrating aortic ulcer.

Through a multidisciplinary approach with our vascular surgery team, we planned the treatment of the patient in our intensive care unit before and after an open surgical replacement of his aneurysm. An endovascular approach was not possible due the complexity of the aortic penetration. Together we decided in a shared decision-making process with the patient for an open aortic repair and preparation for the surgical procedure with the implementation of a lumber cerebrospinal fluid drainage, neurological monitoring with motor evoked potentials during the operation, preconditioning with levosimendan and supporting the circulation of the patient with a veno-arterial extracorporeal membrane oxygenation for the operation.

The patient received an automated lumber cerebrospinal fluid drainage after receiving 1 g of tranexamic acid and 3500 IU of prothrombin complex concentrate after coagulation diagnostics. The device was set to a drain after reaching a pressure over 20 mmHg. These pressure measurements and fluid drainage were preformed to prevent spinal ischaemia/neurological impairment during and after the surgical procedure. Neurological impairment can occur because of insufficient perfusion of the segmental arteries (e.g. spinal ischaemia) that supply the spinal cord during or after the operation. When combined with augmentation of the systemic blood pressure, a cerebrospinal fluid drainage can reduce the risk of a spinal cord injury by increasing the afferent spinal cord blood supply and perfusion through the creation of a low ambient pressure in the subarachnoid space [3].

Levosimendan therapy was initiated to precondition the patient and improve his cardiac function. Levosimendan is a calcium sensitizer that leads to greater inotropy and decrease of pre-load, and afterload, putting less work on the heart. It has been used in patients with acutely decompensated congestive heart failure and is increasingly used in perioperative settings [4]. Administration began with a dose of 0.1 μg/kg/min over 24 h, and changes in the cardiac index were observed through arterial pressure curve analysis.

Our team decided on a surgical cannulation for the veno-arterial extracorporeal membrane oxygenation (Fig. 40.2) during the operative procedure through the femoral vein and artery and insertion of an additional cannula for perfusion of the

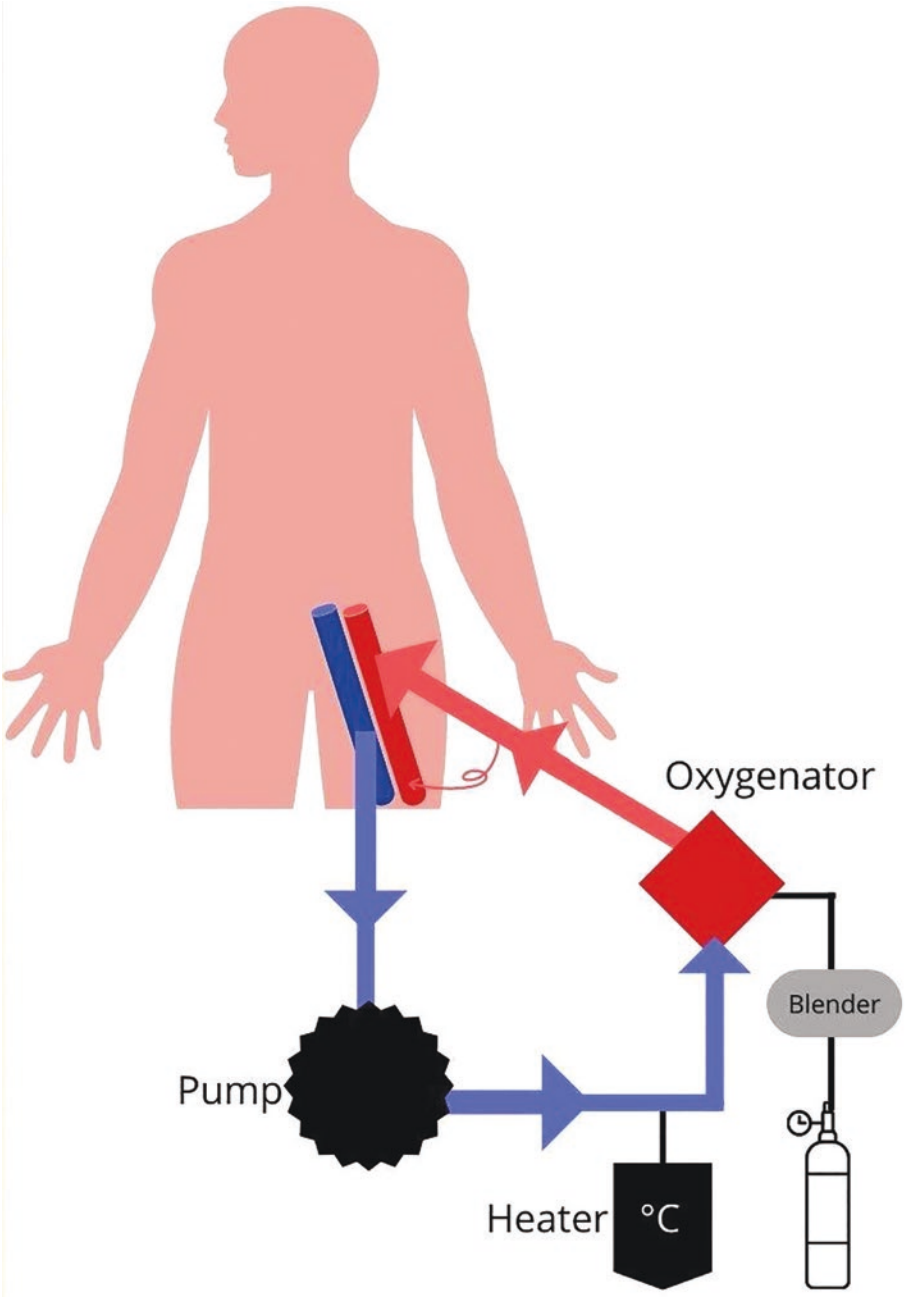

Fig. 40.2 A schematic presentation of the setup used in the patient with an additional cannula for the perfusion of the leg. Two cannulas are placed in large vessels. The machine will drain the blood from the vein, add the oxygen through the oxygenator and remove the carbon dioxide, warm the blood and then return the blood to the artery and pump it the blood through the body. This method allows the blood to bypass the heart and lungs to support the cardiopulmonary function of the patient

leg downstream. The goal to use such a device was to enable cardiopulmonary support during and after the operation for the reduction of possible catecholamine dosing, optimize fluid substitution, avoid ischaemia of the abdominal organs and facilitate early recovery and extubation.

On the third day after admission, the patient received the following surgical procedures under general anaesthesia:

- Thoracolaparotomy
- Open surgical cannulation of the left femoral vein and artery for extracorporeal perfusion
- Additional cannulation of the superficial femoral artery for the perfusion of the leg to prevent limb ischaemia
- Open thoracoabdominal type IV aortic aneurysm repair, a repair procedure between the diaphragm and the aortic bifurcation with a tubular prosthesis (Dacron material)
- Continuous observation of cardiac output by transoesophageal echocardiography and analysis of arterial pressure curves
- Neurological monitoring with motor evoked potentials, without perioperative impairment
- Cerebrospinal fluid drainage of 10 mL once after reaching the intraoperative maximal pressure of 10 mmHg
- Placement of two chest drains on the left side as the thoracic approach carries the risk of lung parenchymal injury especially along the aorta on the left side

The occlusion time of the aortic vessel was 121 min.

Intraoperatively, the veno-arterial extracorporeal membrane oxygenation was set to 2 L/min blood flow, 2000 RPM and a gas flow of 1.5 L/min. The pre-oxygenation pressure was 116 mmHg, and the post-oxygenation pressure was 124 mmHg, a difference of 6 mmHg.

Due to the patient's cardiac history, the team decided to maintain circulatory support with veno-arterial extracorporeal membrane oxygenation. Postoperatively the blood flow and gas flow were reduced to 1.5 L/min and 1 L/min, respectively. After surgery, the patient had to be stabilized with norepinephrine for the next 2 days, with a maximum dose of 0.19 μg/kg/min with a cardiac index of 3.5, which was calculated through a calibrated analysis of arterial pressure curves. The patient received balanced electrolyte solutions and 20 mg furosemide per day to stimulate diuresis and prevent acute kidney injury as the diuresis was decreasing but was still sufficient following the operation.

Anticoagulation was performed with unfractionated heparin intravenously at a dosage of 800 IU/h initially, which was gradually increased to 1300 IU/h to achieve an activated partial thromboplastin clotting time between 50 and 60 s. Heparin was then paused only to remove cerebrospinal fluid drainage.

Enteral nutrition was started after the first day of the operation and was supported by intestinal stimulating medications such as neostigmine (1 mg over 4 h three times per day), lactulose (7.5 mL twice per day) and macrogol (13.1 g once per day). Neostigmine was discontinued on the sixth day after admission, after successful bowel movement and defecation without impairment or signs of intestinal ischaemia.

On the fourth day, transthoracic echocardiography showed a stable ejection fraction of 35%, and the blood floor of the veno-arterial extracorporeal membrane oxy-

genation was decreased to 1.25 L/min. Decannulation was performed on the same day in the operating room for a suture of the cannulate site in the femoral artery. Pacemaker measurements by the cardiology department after the two operations revealed no abnormal events. Catecholamine therapy with norepinephrine was gradually reduced and could be stopped on day 6.

The cerebrospinal fluid drainage was performed through an automated device, which only drained when the pressure around the spinal cord was above 10 mmHg postoperatively. Drainage decreased from 154 mL per day after the initial operation to 45 mL in total on day 5 and ceased after that day, so the drainage was successfully removed on the sixth day after admission, and no neurological impairments were observed.

On the sixth day, the patient was still intubated and presented an increase in infection parameters. A chest X-ray confirmed the suspicion of a ventilator-associated pneumonia, as there were pulmonary infiltrates in the right lower lobe.

After sampling of materials for microbiological examination, a calculated antibiotic therapy with piperacillin and tazobactam was administered at a dosage of 4.5 g three times daily.

On the same day, the patient experienced a generalized seizure. We began treatment with 1500 mg levetiracetam twice per day. A cranial computed tomography was performed and revealed no evidence of pathology related to the seizure. After consulting our neurology department and performing EEG diagnostics, we could not find any signs of epilepsy. Thus, the levetiracetam dosage was reduced to 750 mg/day as the cause of the seizure remained unclear, most likely triggered in the context of infection.

The patient's renal parameters increased from initial 1.1–1.71 mg/dL on the sixth day, with maintained diuresis. Due to acute renal failure, the patient was placed on the dialysis watch list and initially received diuretic therapy with 40 mg of furosemide twice daily; the dose was reduced to 20 mg twice daily after 5 days to. His renal parameters decreased in the following days, and adequate diuresis was maintained.

After an improvement in ventilation and a successful spontaneous breathing trial, the patient was extubated on the seventh day after admission. We continued intensive supportive respiratory therapy, alternating with noninvasive ventilation with continuous positive airway pressure via a facemask and a high flow nasal cannula. The antibiotic therapy was adjusted on day 10 to 500 mg imipenem and 500 mg cilastatin targeted four times daily due to persistent respiratory symptoms and microbiological findings. Oxygenation and gas exchange improved in the following 2 weeks, and the patient was placed on low flow oxygenation therapy with 2 L/min oxygen via a standard nasal cannula.

The prolonged stay on intensive care unit was accompanied by delirium, which was first observed on day 11 in the form of disorientation and agitation. The patient was supported with non-drug measures such through the promotion of good sleeping habits, surrounding with familiar objects, encouragement to eat and move, and excessive support for orientation through our unit's staff and his family. Medication with dexmedetomidine was started at a continuous rate of 0.2 μg/kg/h and later increased to 1.4 μg/kg/h. Subsequently, the patient received quetiapine at an initial dose of 25 mg twice daily, which was gradually increased to 100 mg in the morning and 150 mg in the evening by the 20th day after admission.

On the 20th day after 2 weeks of seizure prophylaxis without any new seizures or further signs of epileptic disease, levetiracetam was discontinued.

After the first operation, the chest tubes showed a continually decreasing amount of serous secretion. The tubes were successfully removed on the 25th and 28th days after admission. X-ray imaging after chest tube removal did not indicate any related pathological findings.

40.5 Evolution, Outcome, and Follow-Up

The patient was transferred to a surgical ward on day 26. At the time of transfer to the surgical unit, he was stable without any catecholamine, had sufficient oxygenation via a standard nasal cannula, could walk and eat independently, had resumed his previous medication and presented no neurological deficits.

Admission in the surgical ward did not accelerate additional symptomatic presentation; therefore, the patient was transferred to a geriatric rehabilitation facility on the 31st day after admission for further therapy and support.

40.6 Discussion

Although levosimendan preconditioning in patients with cardiac disease is well established and has been extensively published [4], only a few cases of perioperative veno-arterial extracorporeal membrane oxygenation support have been reported since the first case report in 1994. With the improvement of the extracorporeal membrane oxygenation devices used to support these patients, an overall survival rate of approximately 40% has been achieved [5]. Given these results and the fact that our patient's condition was an emergency due to a ruptured penetrating aortic ulcer, an increase in perioperative mortality and morbidity due to pre-existing conditions and age is evident [3].

Open aortic replacement is often associated with a number of specific complications that develop after surgery, such as permanent loss of organ function, including renal failure, spinal cord injury, intestinal ischaemia and lower extremity impairment [1, 3].

Our patient did not require dialysis therapy, although he had chronic renal insufficiency before. The abdominal organs are often affected by ischaemia during the operative phase, especially when the use of catecholamines becomes necessary [6]. Our patient showed no relevant clinical signs of ischaemia in the abdominal organs aside from a mild kidney injury.

This case report shows that even elderly high-risk patients can benefit from circulatory optimization before and after high-risk surgery, such as open aortic replacement. The use of such a device should be evaluated using an individual risk-benefit approach, as the placement and operation of a veno-arterial extracorporeal membrane oxygenation device can cause complications such as bleeding and neurological impairment [7].

The placement of veno-arterial extracorporeal membrane oxygenation needs further evaluation and investigation. A standardized procedure should be developed for

cardiac compromised patients, as the use of such a device in the perioperative setting has only been described in a few publications.

Take-Home Messages

- The utilization of veno-arterial extracorporeal membrane oxygenation can support cardiac impaired patients after surgical procedures.
- At-risk cardiac patients need careful cardiac monitoring for procedures such as an aortic replacement.
- High-risk surgical procedures often involve many complications which require intensive care treatment.

Summary

An 81-year-old male patient was admitted to intensive care due to a ruptured penetrating aortic ulcer which required urgent surgical treatment. The patient presented with cardiac impairment, congestive heart failure and an ejection fraction of about 35%. The patient was optimized for surgery through the application of levosimendan and perioperative use of a veno-arterial extracorporeal membrane oxygenation device and was under close cardiac monitoring via echocardiography and arterial pressure waveform analysis.

After an open thoracoabdominal type IV aortic aneurysm repair, the patient could be decannulated from veno-arterial extracorporeal membrane oxygenation support rapidly without any signs of intestinal ischaemia and only a mild acute kidney injury. During his stay in intensive care, the patient suffered from complications due to ventilator-associated pneumonia and delirium. Patient outcome was good as the patient could be transferred without any neurological impairments, organ impairment or any new cardiac events to a surgical ward after 26 days, following his dismissal to a rehabilitation facility on the 31st day after his initial presentation.

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The Best Clinical Cases in Neurocritical Care and Severe Trauma

Contents

Principles and Management of Subarachnoid Haemorrhage

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Contents

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Learning Objectives

- Recognize signs and symptoms of subarachnoid haemorrhage to make appropriate diagnosis.
- Describe treatment options for a ruptured brain aneurysm.
- Summarize management strategies of neurological and systemic complications associated with subarachnoid haemorrhage.

41.1 Definition and Epidemiology of Subarachnoid Haemorrhage

Subarachnoid haemorrhage (SAH) results from bleeding into the cerebrospinal fluid (CSF)-filled cisterns between the arachnoid and pia mater. SAH accounts for 5% of all strokes [1]. A ruptured cerebral aneurysm is the most common cause of SAH; it is found in around 80% of cases. Aneurysmal SAH (aSAH) is a significant cause of morbidity and mortality throughout the world. SAH is associated with a case fatality rate between 26% and 36%, and roughly half of the survivors are left with some persistent neurological deficit [2, 3].

Although the incidence of aSAH varies widely among populations, in a recent systematic review, overall crude SAH incidence was 7.9 (95% CI, 6.9–9.0) per 100,000 person-years [3]. In that review, a high incidence of aSAH was reported in Finland and Japan, while a low incidence was seen in South and Central America as well as Africa [3]. Global aSAH incidence declined by 1.7% (95% CI, 0.6–2.8) annually between 1955 and 2014 [3]. The incidence of aSAH progressively increases with age [3]. In addition, most studies indicate a higher incidence of aSAH in women than in men [2, 3].

41.2 Diagnosis and Assessment

41.2.1 Risk Factors and Prevention of aSAH

In addition to age and female sex, several factors have been associated with an increasing risk of aSAH [2–5]. Risk factors predispose to aSAH by different mechanisms of action such as vessel wall injury and inflammation, the loss of ability to repair vessel wall injury, and haemodynamic stress [4].

Hypertension, cigarette smoking, alcohol abuse, and the use of stimulant drugs such as cocaine have been described as behavioural risk factors for aSAH [2, 4, 5]. It is further possible that diet may influence the risk of aSAH; consumption of a diet rich in vegetables may lower the risk of aSAH [2]. Also, the presence of an unruptured cerebral aneurysm, a history of previous aSAH, family history of aneurysms or aSAH, certain genetic syndromes, and significant life events within the past month may increase the risk of aSAH [2].

Synergistic effects of risk factors are proposed; therefore, prevention or treatment is recommended if identified [4].

41.2.2 Clinical Manifestations of aSAH

aSAH produces a severe, sudden-onset headache that immediately reaches maximal intensity (thunderclap headache). Awake patients usually describe it as 'the worst headache of my life' [2]. The onset of the headache may be associated with other symptoms and signs, including neck pain or stiffness, limiting neck flexion, diplopia, photophobia, nausea, vomiting, dizziness, loss of consciousness, or focal neurological deficits. Seizures may occur in up to 20% of patients after aSAH, most commonly in the first 24 h. Between 10% and 43% of patients have a warning or 'sentinel' headache that precedes the aSAH. This headache occurs 2–8 weeks prior to overt aSAH, and patients may report a milder headache than that associated with a major rupture that may last a few days [2].

Despite the classic presentation of aSAH, individual presentations may occur and lead to misdiagnosis. A high level of suspicion for aSAH should exist in patients with acute onset of severe headache [2].

41.2.3 Clinical and Radiologic Grading

Clinical grading scales have been developed to assess the severity and prognosis based on the initial presentation. The Hunt and Hess scale [6] is useful in correlating the patient's clinical status at admission with prognosis (Table 41.1). The World

Table 41.1 Clinical grading scales of aSAH

Hunt and Hess scale			World Federation of Neurosurgical Societies scale (WFNS)			
Grade	Symptoms	Mortality	Grade	Motor deficit	Glasgow Coma Scale	Risk of severe disability, vegetative state, or death
I	Asymptomatic, or mild headache, alert and oriented, slight (if any) nuchal rigidity	11%	1	–	15	13%
II	Full nuchal rigidity, moderate-severe headache, alert and oriented, no neuro deficit (besides cranial nerve palsy)	26%	2	–	13–14	20%
III	Lethargy or confusion, mild focal neurological deficits	37%	3	+	13–14	42%
IV	Stuporous, more severe focal deficit	71%	4	– or +	7–12	51%
V	Comatose, showing signs of severe neurological impairment (ex: Decerebrate rigidity)	90%	5	– or +	3–6	68%

Table 41.2 Modified Fisher grading scale

Modified Fisher grading scale			
Grade	**IVH**	**SAH characteristics on admission head CT**	**Risk of symptomatic vasospasm**
1	–	Focal thin or diffuse thin SAH	24%
2	+	Absent or focal thin or diffuse thin SAH	33%
3	–	Focal thick or diffuse thick SAH	33%
4	+	Focal thick or diffuse thick SAH	40%

Abbreviations: IVH Intraventricular haemorrhage, *SAH* Subarachnoid haemorrhage

Federation of Neurosurgical Societies (WFNS) [7] uses the combined Glasgow Coma Scale along with clinical motor deficit to estimate the likelihood of poor outcomes (Table 41.1).

The modified Fisher grading scale [8] is the preferred radiologic score currently use. It states SAH severity and helps to predict the risk of clinical vasospasm and delayed cerebral ischemia (DCI) in aSAH based on the amount of blood and clot thickness on head CT. It improves upon the original Fisher scale by incorporating the presence of intraventricular haemorrhage (IVH) (Table 41.2).

41.2.4 Diagnosing a Subarachnoid Haemorrhage

Non-contrast head computed tomography (CT) is the first-line diagnostic test for a suspected SAH [2, 9, 10]. If the initial CT is nondiagnostic, it should be followed by lumbar puncture [2]. SAH will be diagnosed when the lumbar puncture sample shows xanthochromia.

When SAH diagnosis is confirmed, CT angiography (CTA) may be considered to identify the cause of bleeding and guide treatment [2, 9]. However, digital subtraction catheter angiography (DSA) with three-dimensional reconstructions (Fig. 41.1) is still the gold standard diagnostic tool for detecting aneurysms [9] and it is still recommended (except in the case of classic perimesencephalic aSAH) [2]. Magnetic resonance imaging remains inferior to DSA and CTA for aneurysm detection [9].

Fig. 41.1 Shown is a 3D reconstruction of a large aneurysm in the bifurcation of the left internal carotid artery (arrows)

41.3 Management of aSAH

Patients with SAH should be managed at high-volume centres that have neurovascular teams and neurocritical care units [2, 9]. Patients should be admitted into an ICU, and general measures initiated according to current guidelines [2] such as nimodipine administration for 21 days, haemodynamic and volume status monitoring, aggressive control of fever, careful glucose, and ion blood levels management.

41.3.1 Aneurysm Repair

Ruptured aneurysm should be repaired as soon as possible in most patients to reduce the rate of rebleeding after aSAH. Aneurysm treatment should be a multidisciplinary decision made by experienced neurosurgeons and interventionalists, based on the patient's characteristics and the aneurysm [2].

Endovascular coiling (Fig. 41.2) is preferred when ruptured aneurysms are technically feasible to both endovascular coiling and neurosurgical clipping. In patients >70 years of age, in those presenting with poor grade (WFNS classification IV/V) aSAH, and in those with posterior circulation aneurysms, endovascular coiling preference is given. Microsurgical clipping should be preferred in patients presenting with large (>50 mL) intraparenchymal haematomas or middle cerebral artery aneurysms [2].

Although the complete obliteration rate can be increased by the addition of a stent, this is associated with increased morbidity and mortality [2].

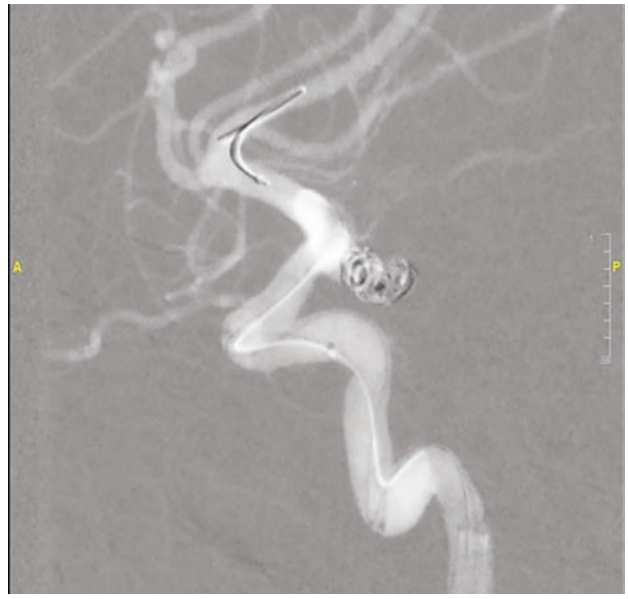

Fig. 41.2 Endovascular coiling

41.4 Neurological Complications

41.4.1 Vasospasm and Delayed Cerebral Ischemia

Vasospasm is the narrowing of cerebral arteries which can be detected on CT, magnetic resonance, or DSA [11]. Vasospasm occurs most frequently 7–10 days after aneurysm rupture and resolving spontaneously after 21 days. It can occur at multiple levels in the arterial and arteriolar circulation. Delayed cerebral ischemia (DCI) is defined as any neurologic deterioration that persists for more than 1 h and cannot be explained by any other neurologic or systemic condition [11]. Both conditions are related, but it is not necessary that they appear together. Cerebral infarction from DCI represents the leading cause of morbidity and mortality in patients surviving initial aneurysmal subarachnoid haemorrhage. The most important factors that contribute to DCI are the volume, location, density, and clearance rate of aSAH and intraventricular haemorrhage [12].

Although several treatments to prevent vasospasm have been studied, to date, oral nimodipine is the only treatment that is recommended generally for all patients with aSAH [2]. This agent has been shown to improve neurological outcomes but not cerebral vasospasm. Furthermore, maintenance of euvolemia and normal circulating blood volume is recommended to prevent DCI [2].

Diagnostic approach of DCI needs to be adapted to the clinical situation. Monitoring for vasospasm includes frequent neurologic examinations. Diagnostic tools should identify arterial narrowing and/or perfusion abnormalities or reduced

brain oxygenation. Transcranial Doppler is reasonable to monitor for the development of arterial vasospasm assessing the arterial mean flow velocity and calculating the Lindegaard ratio [2, 13]. The Lindegaard ratio refers to the calculated ratio of the mean flow velocities in the middle cerebral artery and the ipsilateral extracranial internal carotid artery. Perfusion imaging with CT or magnetic resonance can be useful to identify regions of potential brain ischaemia [2].

If DCI develops, rescue therapies are recommended. To improve cerebral perfusion, besides the maintenance of euvolemia, the induction of hypertension is recommended unless cardiac status precludes it [2]. In patients with symptomatic cerebral vasospasm who do not improve with the induction of hypertension, or the patient cannot tolerate it, then endovascular treatment by cerebral balloon angioplasty or selective intra-arterial vasodilator therapy is recommended [2]. Balloon angioplasty is usually used for accessible lesions and vasodilator therapy for more distal vessels.

41.4.2 Hydrocephalus

Hydrocephalus can develop because of impaired cerebrospinal fluid (CSF) reabsorption or the presence of an intraventricular clot obstructing CSF outflow.

Clinically, significant acute hydrocephalus should be managed by external ventricular drainage (EVD) or lumbar drainage, depending on the clinical scenario [2]. EVD is generally associated with neurological improvement. Although lumbar drainage has been reported to be safe, EVD should be preferred when obstructive hydrocephalus is suspected.

Chronic hydrocephalus associated with aSAH should be treated with ventricular shunt placement.

41.4.3 Rebleeding

Aneurysm rebleeding is a serious and frequent complication of SAH. It is associated with very high mortality and poor prognosis in survivors. Between the first 2 and 12 h, the risk of rebleeding is maximal, and early rebleeding is associated with worse outcome than later rebleeding [2].

Clinical symptoms of rebleeding include sudden increase in headache, seizure, nausea, vomiting, depressed level of consciousness, and new neurologic deficits. Factors associated with aneurysm rebleeding include longer time to aneurysm treatment, worse neurological grade on admission, initial loss of consciousness, previous sentinel headaches, higher blood pressure (systolic blood pressure >160 mmHg), intraventricular or intracerebral haemorrhage, and larger aneurysm size [2, 9].

Prevention of rebleeding may be achieved by treating acute hypertension after aSAH until aneurysm obliteration but, most importantly, by repairing the aneurysm as soon as possible. Short-term (<72 h) therapy with antifibrinolytic drugs should be considered to reduce the risk of early aneurysm rebleeding for patients with an unavoidable delay in obliteration of aneurysm, a significant risk of rebleeding, and no compelling medical contraindications [2, 9].

41.4.4 Seizures

Seizures associated with SAH may increase the risk for rebleeding from an unsecured aneurysm; however, their management is controversial.

Current guidelines suggest considering the use of prophylactic anticonvulsants in the immediate posthaemorrhagic period [2]. However, studies on the use of anticonvulsants, in particular, phenytoin, showed association with worse neurologic recovery [14]. Thus, anticonvulsants should be stopped as soon as the aneurysm has been repaired if the patient is not comatose and has a consistent neurologic examination [2]. Although routine long-term use of anticonvulsants is not recommended, continuation of anticonvulsants may be justified for patients with known risk factors for delayed seizure disorder, such as a prior seizure at SAH onset, intracerebral haematoma, intractable hypertension, infarction, or aneurysm at the middle cerebral artery [2]. Another factor that may influence the development of seizures is the type of treatment of the ruptured aneurysm. Significantly lower incidence of seizures was demonstrated in patients treated with endovascular coiling [15].

41.5 Systemic Complications

Spontaneous SAH patients can suffer not only from various neurological complications but also multiple systemic complications [16]. Systemic complications after SAH are common and lead to an attributable mortality of 23% [17].

The most common medical complication in aSAH is the fever of central origin. This complication has been associated with the severity of injury, amount of haemorrhage, development of vasospasm, and with worse cognitive outcomes. Consequently, aggressive control of fever to target normothermia by using standard or advanced temperature modulating systems in the acute phase of aSAH is recommended [2].

Anaemia is common after aSAH and may compromise brain oxygen delivery. The optimal haemoglobin threshold for transfusion after aSAH is not yet known and varies from 70 to 120 g/L. Nonetheless, the use of packed red blood cell transfusion to treat anaemia might be reasonable in patients with aSAH who are at risk of cerebral ischemia [2].

Hyponatremia is frequently observed in the acute phase after aSAH and can develop from different mechanisms. The cerebral salt wasting syndrome is characterized by excessive renal loss of sodium leading to hyponatremia and a decrease in extracellular fluid volume. This syndrome is more common in patients with poor clinical grade, ruptured anterior communicating artery aneurysms, and hydrocephalus, and it may be an independent risk factor for poor outcome. Following current guidelines, the use of fludrocortisone acetate and hypertonic saline solution is reasonable for preventing and correcting hyponatremia [2].

Cardiac complications associated with SAH are diverse, appear in the initial phase, and are temporary in most cases. Due to excessive sympathetic stimulation, cardiac dysrhythmias and stress cardiomyopathy are often seen. In fact, SAH is the most frequent neurologic cause of electrocardiographic changes.

In high-grade SAH after aneurysm rupture, the excessive sympathetic stimulation can also affect the lung by stimulating β-receptor. This can lead to sudden and early neurogenic pulmonary oedema associated with severe hypoxaemia. Although this pulmonary complication is transient during the first 24–48 h, it should be recognized early, and diuretic treatment should be initiated as soon as possible.

Take-Home Messages

- Subarachnoid haemorrhage is a significant cause of morbidity and mortality throughout the world.
- Early identification and repair of the ruptured aneurysm, preferably by endovascular coiling, is indicated to prevent rebleeding.
- Microsurgical clipping should be preferred in patients presenting with large intraparenchymal hematomas or middle cerebral artery aneurysms.
- Oral nimodipine and endovascular aneurysm repair are the only treatments based on higher level of evidence.
- Only clinically symptomatic vasospasm should be treated with the induction of hypertension and endovascular treatment.
- Clinically significant acute hydrocephalus should be managed by external ventricular drainage.
- Prophylactic anticonvulsants are only recommended in the immediate posthaemorrhagic period and should be stopped as soon as the aneurysm has been repaired.
- There are pathological changes in virtually every organ system after SAH. Systemic complications associated with SAH should be recognized early and treated accordingly.

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Systemic Complications of Subarachnoid Hemorrhage: A Case Report

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Contents

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Learning Objectives

- Intensive care unit management of a subarachnoid hemorrhage after aneurysmal rupture.
- Systemic complications of acute brain injury.
- Treatment of pulmonary embolism.
- Investigation of the mutation of coagulation factors.

42.1 Introduction

Spontaneous aneurysmal subarachnoid hemorrhage is a major cause of mortality and prolonged disability. The functional outcome after subarachnoid hemorrhage is affected by the severity of initial bleeding, as well as by further neurologic complications such as rebleeding, vasospasm, delayed ischemia, and hydrocephalus, among others. Additionally, a rapid rising of intracranial pressure after intracranial bleeding can occur [1], causing a drop of the cerebral perfusion pressure, whereas the altered vascular tone may lead to transient cerebral ischemia [2]. In addition to disease-specific neurologic complications, patients with subarachnoid hemorrhage may manifest systemic complications that are frequently associated with prolonged bed rest and patients' comorbidities. Venous thromboembolism may manifest itself as deep venous thrombosis or pulmonary embolism that might be responsible for myocardial infarction or stroke. The pathophysiology of pulmonary embolism includes the failure of the right ventricle with decreased cardiac output, followed by altered circulation and gas exchange [3]. A prompt diagnosis and therapy should be made as soon as possible if pulmonary embolism is highly suspected [3]. Other pulmonary complications following acute brain injury have been described in the literature, including ventilator-associated pneumonia, acute respiratory distress syndrome, and neurogenic pulmonary edema. The prevention and treatment of cardiopulmonary complications in patients with acute brain injury is a crucial step since the interplay among the brain, the heart, and the lung is complex and may impact on patient outcome. Therefore, the primary goal in the management of subarachnoid hemorrhage is to prevent rebleeding using a neurosurgical or endovascular approach [2]. Secondary goals include an advanced critical care management to prevent possible neurologic and systemic complications [4]. The aim of this case report is to discuss the difficult management of a patient with subarachnoid hemorrhage due to aneurism rupture who manifested pulmonary embolism as a systemic complication after acute brain injury.

Case Presentation

A 41-year-old Caucasian male (height, 175 cm; weight, 75 kg; body mass index, 24.4 kg/m^2) who manifested headache and vomited after effort was admitted to the emergency department of a spoke hospital. Patient anamnesis didn't include chronic pathologies, medications, allergies, and domiciliary treatments. After the admission to the emergency department, the patient was hemodynamically monitored (including electrocardiography, peripheral oxygen saturation, and noninvasive blood pressure) and neurologically investigated. Cerebral-computed tomography and angio-computed tomography demonstrated the rupture of an aneurysm located in the right middle cerebral artery bifurcation (M1–M2 tract). Hunt and Hess scale score was 3/5; the World Federal Neurosurgical Societies score was 4/5. During the diagnostic investigations, the patient was intubated due to the worsening of consciousness (Glasgow Coma Scale <9/15) and connected to a mechanical ventilator. Hence, the patient was transferred to the hub-referring hospital for treating the ruptured aneurismatic malformation and for receiving comprehensive and advanced neurocritical care. During the intensive care unit stay, the patient manifested pulmonary embolism and was treated accordingly.

42.2 Investigations

42.2.1 Emergency Department of the Spoke Center

The following blood tests were performed: biochemical tests, coagulation, blood cell count, and severe acute respiratory syndrome coronavirus-2 test. A cerebral-computed tomography and angio-computed tomography demonstrated a subarachnoid hemorrhage Fisher grade III due to the rupture of an aneurysm of the right middle cerebral artery at the bifurcation level. After proceeding with sedation, endotracheal intubation, and mechanical ventilation, the patient was transferred to the hub center.

42.2.2 Emergency Department of the Hub Center

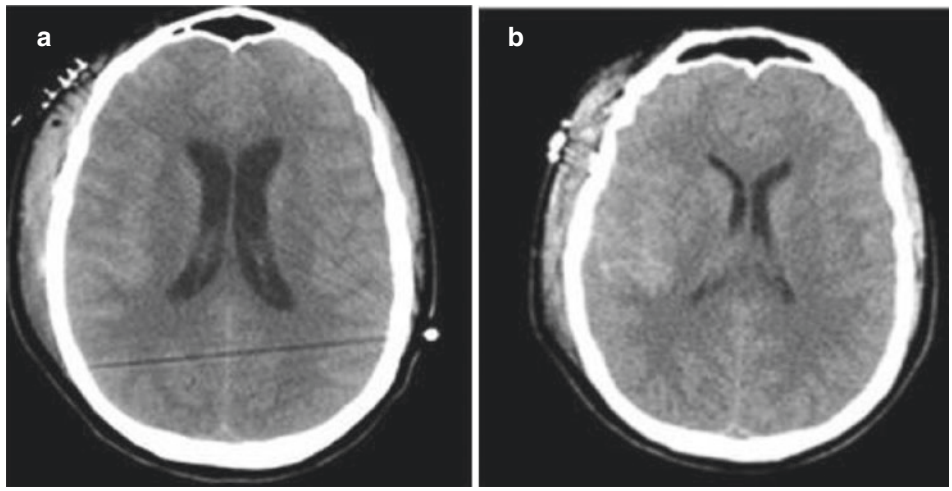
The patient arrived at the emergency department of the hub-referring center, sedated, intubated, and mechanically ventilated. An invasive arterial catheter was placed to have a continuous monitoring of the arterial blood pressure. A central venous catheter was also inserted. A lung-protective mechanical ventilation strategy with low tidal volume (6–8 mL/kg of predicted body weight) and protective pulmonary pressures was initiated. The ventilatory setting was monitored with gas exchange. A urinary catheter to measure the urinary output and a gastric tube were also placed. Biochemical and analytic blood investigations were performed. A new angio-computed tomography confirmed the diagnosis, and after consulting with the neuroradiologists, the neurosurgeons treated the aneurysm by clipping.

42.2.3 Intensive Care Unit

During intensive care unit stay, the patient was continuously investigated for neurological, hemodynamic, and respiratory status. Renal and hepatic function were also assessed, as well as fluid balance, nutritional status, coagulative system, endocrine system, biochemical analysis, and cultural microbiological investigations.

42.2.3.1 Neurological Investigations

Following the aneurysmal treatment, the patient was admitted to the intensive care unit. During the intensive care unit stay, the patient was gradually awakened to investigate the neurological status. Twelve hours after the neurosurgical treatment, a brain-computed tomography was performed (◘ Fig. 42.1a): An initial dilatation of the ventricular system appeared, but there was no evidence of new neurological complications. Twelve hours thereafter, a further computed tomography was performed: The alteration of the ventricular system disappeared, whereas a small focal edema surrounded the surgical area, and no other complications were found (◘ Fig. 42.1b). To exclude the presence of vasospasm, a transcranial Doppler was performed after the surgery, 24 h thereafter, and every 12 h without finding signs of mass effect, hydrocephalus, hyperemia, or vasospasm; further periodical transcranial Doppler sonographies resulted in normal for Lindegaard ratio and signs of vasospasm or hyperemia.



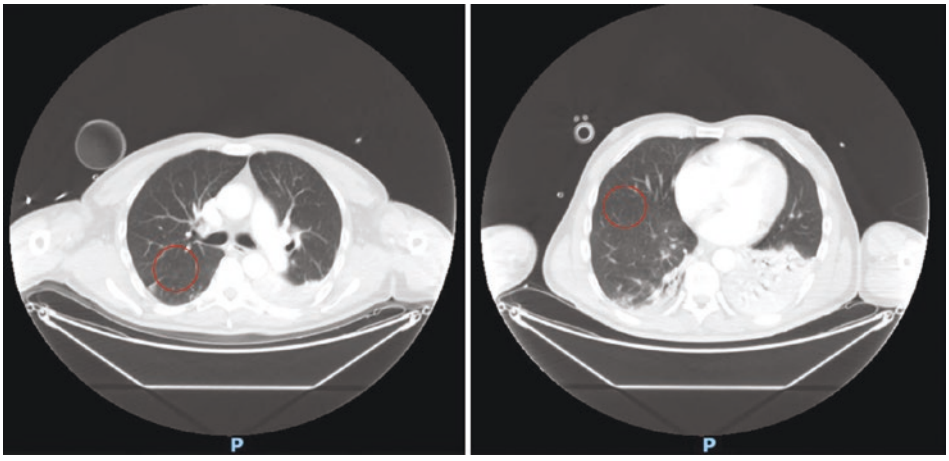
◘ **Fig. 42.1** This figure depicts two brain-computed tomography images performed 12 h after the neurosurgical treatment (**a**) and 12 h thereafter (**b**). Twelve hours after the neurosurgical treatment, an initial enlargement of the ventricular system was found without intracranial complications (first scan on the left). No intracranial complications or pathological evolution were detected 12 h after the first scan (second scan on the right)

42.2.3.2 Hemodynamic Monitoring

Hemodynamic parameters (mean arterial pressure, mean arterial pressure waveform, and heart rate) were monitored continuously. Twenty-four hours after the intensive care unit admission, an electrocardiogram was performed showing sinus bradycardia and regular ventricular function. An echocardiogram was performed because of the impairment of gas exchange after extubation, finding initial right ventricle dilatation, decreased right ventricle fractional area, minimal tricuspid regurgitation, hyperdynamic left ventricle, and initial pulmonary artery dilatation (echocardiogram was not performed by echocardiography specialists).

42.2.3.3 Pulmonary Investigations

Mechanical ventilation parameters were monitored at least three times a day, and gas exchange was assessed at least three times a day. After a worsening of the gas exchange following extubation, an angio-chest-computed tomography was performed (◘ Fig. 42.2), finding a central filling defect within the peripheral vessel of the right lung surrounded by contrast material. The pulmonary embolism was treated accordingly, and a new brain and chest-computed tomography was performed to assess the efficacy of the treatment and eventual cerebral rebleeding. The images resulted negative for rebleeding while still positive for pulmonary embolism. The vascular surgeon performed an echo color Doppler of the lower limbs excluding the presence of deep venous thrombosis. To further understand the etiology of the pulmonary embolism, we investigated the coagulation factors, finding a mutation of lupus anticoagulant and the presence of antibodies anti endothelium. D-dimer was as high as 6,654 mcg/L [normal value: 0–500] during the acute phase. During the intensive care unit course, the patient was suspected of ventilator-associated pneumonia by radiologic and clinical criteria. Some bronchoscopies were performed to collect microbial samples, demonstrating a normal mucosa and mucopurulent secretions, but no pathogens could be isolated.



◘ **Fig. 42.2** In the angio-chest-computed tomography defects of perfusion were found in the peripheral ramifications of the right pulmonary artery

42.3 Differential Diagnosis

The differential diagnosis included ventilator-associated pneumonia, aspiration pneumonia, and pulmonary embolism. Differential diagnoses were excluded apart from pulmonary embolism using radiological diagnostics.

42.4 Treatment

42.4.1 Emergency Department of the Hub Center

The patient arrived at the emergency department of the hub-referral hospital sedated, intubated, mechanically ventilated, and fully monitored. Regarding the neurosurgical treatment, the aneurysm was treated by clipping 4 h after the admission to reduce the risk of rebleeding. Mean arterial pressure and heart rate were maintained within normal ranges to guarantee a good cerebral perfusion. Urinary output was maintained at least 1 mL/kg/h through balanced crystalloid infusion. The patient was mechanically ventilated with the following parameters: pressure-controlled ventilation; ventilation pressure, 19 cmH_2O; positive end-expiratory pressure, 5 cmH_2O; fraction of inspired oxygen, 40%; respiratory rate, and 17 breaths/min; which resulted in a tidal volume of 7.33 mL/kg. Analytic exams were normal, so there was no need for blood or plasma transfusion or therapy of coagulation. The glycemia was normal, without a need for adjustment by insulin or glucose infusions.

42.4.2 Intensive Care Unit

42.4.2.1 Neurological Treatment

Upon the neurosurgical treatment, the patient was admitted to the intensive care unit, sedated with propofol continuous infusion and in analgesia with fentanyl. An early neurological examination demonstrated no neurological impairment, but altered pupillary motor reflex (right eye, 33%; left eye, 8%) at automated pupillometry, the patient executed easy commands and answered the operator moving the head. Twenty-four hours after the accident, a new brain-computed tomography was assessed, without needing to do further neurosurgical treatment. Transcranial Doppler ultrasound confirmed no need for further interventions. Continuous infusion of nimodipine 2 mg/h was started to prevent vasospasm and continued for 21 days. Seizures prophylaxis with intravenous levetiracetam 1,000 mg q12 hours was started to prevent seizure after craniotomy and neurosurgical intervention.

42.4.2.2 Hemodynamic Management

Continuous infusion of balanced crystalloids and norepinephrine was started to reach a target systolic arterial pressure of 120–140 mmHg. Mechanical thrombus prophylaxis with pneumatic legging was started.

42.4.2.3 Pulmonary Treatment

The mechanical ventilation was switched to pressure support ventilation: pressure support, 8 cmH_2O; positive end-expiratory pressure, 6 cmH_2O; fraction of inspired oxygen, 40%; and respiratory rate, 14 breaths/min, resulting in a tidal volume of 6–8 mL/kg. After 48 h, the patient was weaned from the mechanical ventilator and successfully extubated. Oxygen was administered with a Venturi mask with a fraction of inspired oxygen of 60%. However, the arterial oxygen tension rapidly decreased to 45 mmHg, and noninvasive ventilation with a full-face mask was started achieving partial benefit (pH = 7.47; arterial partial pressure of oxygen, 64 mmHg; arterial carbon dioxide tension, 37.9 mmHg; and an arterial partial pressure of oxygen/fraction of inspired oxygen ratio, 80). Previously sedated and paralyzed with rocuronium 80 mg, the patient was orotracheally intubated and mechanically ventilated in pressure control ventilation with the following parameters: pressure control, 15 cmH_2O; positive end-expiratory pressure, 5 cmH_2O; fraction of inspired oxygen, 100%; and respiratory rate, 12 breaths/min, resulting in a tidal volume of 6–8 mL/kg. The blood gas analysis showed the following results: pHa, 7.44; arterial partial pressure of oxygen/fraction of inspired oxygen ratio, 72.6; and arterial carbon dioxide tension, 41.9 mmHg. Because of the respiratory worsening in clinical presentation, pulmonary embolism or ventilator-associated pneumonia was suspected. After the diagnosis of pulmonary embolism, continuous infusion of heparin was started with a bolus of 4,500 IU, followed by continuous infusion of 900–1350 IU/h, monitoring periodically (every 6 h) with activated partial thromboplastin time, targeting a value of 55–65 s. Three days later, we switched to enoxaparin 6,000 IU q12 hours. For the suspect of pneumonia, linezolid 600 mg q12 hours and meropenem 2 gr q8 hours were empirically administered, lasting 10 days of treatment.

42.4.2.4 Other Treatments

According to patient critical care management, enteral nutrition via nasogastric tube and supportive parenteral nutrition (due to gastric stagnation) were started on the first day; hence, enteral nutrition was continued with a target of 25–30 kcal/kg/day.

42.5 Evolution, Outcome, and Follow-Up

Subarachnoid hemorrhage was complicated by pulmonary embolism and suspicion of ventilator-associated pneumonia, which was treated with an empirical antimicrobial therapy, but no pathogen was isolated. Upon 14 days of mechanical ventilation and difficult weaning due to delirium appearing after lowering the sedation, we performed a percutaneous tracheostomy. Following the tracheostomy, we were able to reduce propofol and fentanyl continuous infusions. The patient was weaned using pressure support ventilation. Twenty-four hours after tracheostomy, the respiratory support was switched to high-flow nasal cannula treatment (flow = 55 L/min; fraction of inspired oxygen = 45%). Neurological exam was negative (Glasgow Coma Scale, 15/15), excluding the pupillary reflex of the left eye that remained altered and headache. The patient referred to the incapacity of recognizing forms with the left eye, so an ophthalmologic evaluation was assessed, which was negative for hemorrhage or

fundus alterations. A physiotherapy rehabilitation was started, and in 2 weeks, the patient was able to walk alone with the help of a walker. At the time of intensive care unit discharge, Glasgow Outcome Scale was 5/5, and Glasgow Outcome Scale extended was 7/8. The patient was transferred to a rehabilitation ward where he continued physiotherapy treatment, which lasted 10 days more, allowing the patient to be discharged at home with a minimal disability related to the ocular complication.

42.6 Discussion

This clinical case wants to highlight the existence of a brain-lung crosstalk and discuss the management of pulmonary complications after subarachnoid hemorrhage [5]. We report a patient who presented subarachnoid hemorrhage complicated by pulmonary embolism and suspicion of ventilator-associated pneumonia. The patient was diagnosed of subarachnoid hemorrhage due to aneurysm rupture. According to the guidelines, after the impairment of consciousness, he was intubated and transferred to a hub center to undergo neurosurgical treatment [2]. The patient was monitored for neurological changes several times a day. Sequential transcranial Doppler and brain-computed tomography were assessed [1, 4]. Norepinephrine continuous infusion and fluid replacement were initiated to maintain adequate cerebral perfusion, and nimodipine was started to reduce the risk of vasospasm. Fluid balance was closely monitored [4]. Hyperthermia was prevented using cold fluid and pharmacological treatment [4]. Despite no clear evidence regarding prophylactic anti-seizure therapy, we administered anti-seizure medications due to the evidence of high-risk neurosurgical procedures. We assessed the coagulation profile of the patient daily, proceeding to blood transfusion if hemoglobin lowered below 8 g/dL [1]. Few hours after extubation, the gas exchange worsened, raising the suspicion of ventilator-associated pneumonia or pulmonary embolism. Given that the positive predictive value of elevated D-dimer is low [3], an echocardiogram was performed [3], demonstrating a dilated right atrium and right ventricular with massive tricuspid reflux; for this reason, a chest-computed tomography was assessed confirming the diagnosis of pulmonary embolism. Echo color Doppler of the lower limbs was found negative. According to the guidelines, we started early invasive respiratory support at the onset of pulmonary embolism. Unfractionated heparin was administered for those at high risk of acute instability [3]. Despite intracranial bleeding was stable, we did not use a thrombolytic treatment according to the guidelines [3]. After the acute phase of the disease, enoxaparin treatment was initiated. Additionally, an early broad-spectrum antimicrobial therapy was initiated for the suspicion of ventilator-associated pneumonia. We investigated alterations in coagulation factors, diagnosing both the presence of lupus anticoagulant and antibodies anti endothelium. Patient outcome was good with a minimal disability related to the ocular complication.

In summary, this case is a clear example of brain-lung interplay after acute brain injury. Major pulmonary complications are frequent after acute brain disorder, and an adequate management and treatment of these systemic conditions is pivotal for achieving a good patient outcome. The presence of altered factors of the coagula-

tive cascade may explain why our patient was at higher risk of developing cardiopulmonary complications. This is in accordance with the "double hit model," for which inflammatory cytokines that are produced after a brain injury cross the blood-brain barrier and spread to the systemic circulation, thus affecting organs and systems, which are more susceptible to invasive procedures and pathophysiological alterations [5].

Take-Home Messages

- In patients with acute brain injury and neurological worsening, protect the airways with orotracheal intubation to reduce the risk of pneumonia and to guarantee adequate systemic and brain oxygenation.
- Neurosurgical or neuroradiological treatment of subarachnoid hemorrhage reduce the risk of rebleeding.
- Subarachnoid hemorrhage needs a specialized neurointensive care to prevent and manage its possible systemic complications.
- A multidisciplinary evaluation and adherence to the guidelines is mandatory to guarantee the best quality of care.

Summary

Subarachnoid hemorrhage may manifest with a broad clinical spectrum of symptoms; hence, it is important to perform a rapid diagnostic imaging when the clinical suspicion is high. Correct airway management is crucial to reduce the risk of pneumonia and guarantee adequate blood oxygenation to target cerebral oxygen requirements. Neurosurgical or neuroradiological treatment lowers the risk of rebleeding, while a specialized neurointensive care management is crucial to reduce the risk of developing systemic complications. Multiple daily assessments of general patient status are paramount and permit to intervene on time. The correct timing for assessing computed tomography is crucial for neurological outcomes as well as the monitoring of complications with noninvasive neuromonitoring tools like transcranial Doppler. Thromboprophylaxis should be immediately started to reduce the risk of deep vein thrombosis and pulmonary embolism, targeting both the hemorrhagic diathesis of the primary pathology and the possible thrombotic complications. In case of pulmonary embolism, the primary goal is to guarantee adequate blood oxygenation proceeding with intubation and mechanical ventilation to target optimal brain oxygenation. The origin of the embolism should be identified, and the treatment should be rapidly started. Hemodynamic monitoring and management should guarantee adequate tissue and brain perfusion. Weaning and extubation should be performed when the gas exchange, respiratory mechanics, and neurological status allow it. Alterations of the coagulation factors should be investigated if no reasonable explanation for the embolism is found.

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Cardiovascular Complications of SAH: Neurogenic Stunned Myocardium in Subarachnoid Haemorrhage

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Contents

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Learning Objectives

- Recognize signs and symptoms of neurogenic stunned myocardium to make appropriate diagnosis.
- Identify aneurysmal subarachnoid haemorrhage as a cause of neurogenic stunned myocardium.
- Utilize knowledge regarding subarachnoid haemorrhage to order appropriate imaging and to provide the adequate treatment.

43

43.1 Introduction

Subarachnoid haemorrhage (SAH) is a threatening condition caused by the rupture of an intracranial aneurysm in most of the cases. It is responsible for around 5% of all strokes but tends to affect younger people, which result in a greater loss of productive life [1]. SAH is associated with significant morbidity and mortality. It has a mortality rate of up to 50%, and among the survivors, half suffer from cognitive impairment that affects their quality of life, and a third are dependent on long-term care facilities. The most common symptom is a sudden onset of severe headache with or without neurologic deficit; however, atypical symptoms exist making the diagnosis difficult. Patients can experience chest pain, syncope, or even cardiac arrest at onset.

Spontaneous SAH patients can suffer not only from various neurological complications, such as vasospasm, rebleeding, or hydrocephalus but also multiple systemic complications. All of them have an associated mortality similar to the initial bleeding, so their prevention, diagnosis, and treatment are very important. Systemic complications after SAH are common and lead to an attributable mortality of 23% [2]. Cardiac complications associated with SAH are diverse, appear in the initial phase, and are temporary in most cases. They can mimic myocardial ischaemia in some cases, making the diagnosis more difficult, and they have an impact on the clinical course and outcome.

This case highlights the potential severity of the cardiac manifestations of subarachnoid haemorrhage as well as the need to consider an acute neurological disease as a cause of electrocardiographic or echocardiographic abnormalities and troponin elevation, suggestive of myocardial infarction, in order to avoid possible inappropriate or delayed therapy. In cases without symptoms of acute coronary syndrome, or with a history of severe headache, potentially harmful antiplatelet and anticoagulation therapies should be delayed until we can prove a coronary artery disease involvement.

Case Presentation

A 56-year-old woman was brought to the emergency department (ED) by the emergency medical services (EMS) after having experienced loss of consciousness at home. She was a regular smoker with no comorbid disease in her past medical history or recreational drug use. When the EMS arrived at the scene, the patient was unconscious with isochoric and reactive pupils, extensor response to noxious stimuli, and absence of verbal or eye-opening response. The family was interviewed; they said that the patient experienced sudden chest pain and headache before losing conscience. First vital signs were blood pressure (BP) of 210/113 mmHg, heart rate (HR) of 85 bpm, and oxygen saturation (SpO_2) of 95%. The patient was intubated and transported to the ED.

In the ED, BP was 88/63 mm Hg; HR, 100 bpm; and SpO_2, 95%. Heart sounds were regular with no murmurs, and the lungs were clear to auscultation bilaterally. Glasgow Coma Scale was 3, and pupils were miotic with adequate pupillary response. The patient was receiving analgosedation (boluses of midazolam and fentanyl) and balanced crystalloid as resuscitation fluids.

43.2 Investigations

The electrocardiogram (ECG) showed a sinus rhythm with 98 bpm, ST-segment elevation in lead V3 and ST-segment depression with negative T wave in leads II, III, aVF and V4 to V6 (Fig. 43.1). She had a normal chest X-ray.

Laboratory test showed a mixed metabolic acidosis (pH, 7.24; pCO_2, 44 mm Hg; HCO_3, 20.3 mEq; lactate 2.8 mmol/L) in the arterial blood gas and increased levels of high-sensitive cardiac troponin T and brain type natriuretic peptide in the biochemistry (Table 43.1).

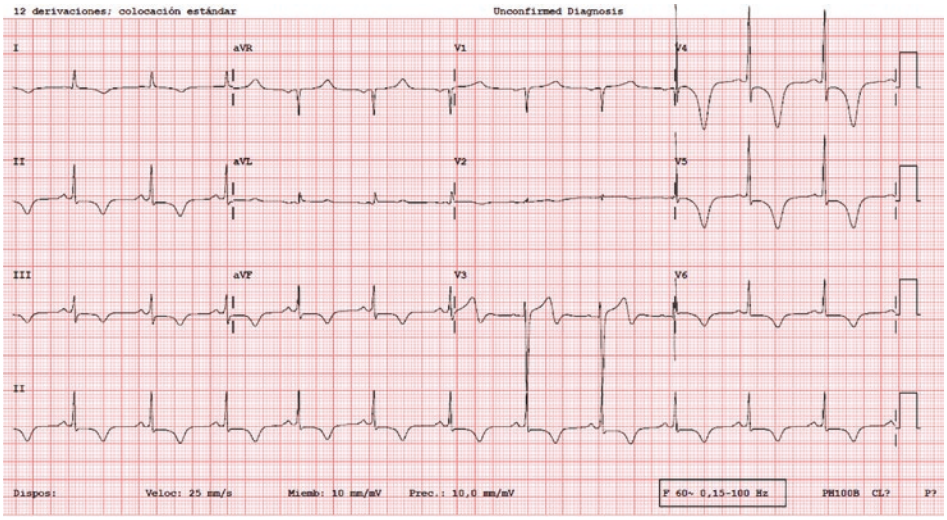

Fig. 43.1 ECG in the ED

Table 43.1 Vital signs, inotropes doses, transpulmonary thermodilution values, relevant laboratory test results from onset until 72 h after ICU admission

Time	Vital signs	Inotropes	Haemodynamic monitoring	Biochemistry/blood gas test
Home	BP: 210/112 mmHg HR: 85 bpm $SatO_2$: 95%			
Emergency Department	BP: 88/63 mmHg HR: 100 bpm SatO2: 98%			pH: 7.24 pCO_2: 44 mmHg pO_2: 123 mmHg HCO_3: 20.3 mEq Lactate: 2.8 mmol/L
ICU Admission	BP: 115/66 mmHg HR: 75 bpm $SatO_2$: 98%	NE 0.8 mcg/kg/min	CI: 1.1 L/min/m^2 SVRI: 4500 dyn*s*cm^{-5}*m^2 GEDI: 686 mL/m^2 EVLWI: 10 mL/kg	CPK: 155 UI/mL Myoglobin: 217 ng/mL Hs-cTn: 78.48 ng/L NT-proBNP: 433 pg/mL
ICU 12 h	BP: 120/73 mmHg HR: 72 bpm $SatO_2$: 94%	NE 0.5 mcg/kg/min Dobutamine 5 mcg/kg/min	CI: 2 L/min/m^2 SVRI: 3800 dyn*s*cm^{-5}*m^2 GEDI: 600 mL/m^2 EVLWI: 15 mL/kg	CPK: 144 UI/mL Myoglobin: 30 ng/mL Hs-cTn: 354 ng/mL NT-proBNP: 3244 pg/mL
ICU 36 h	BP: 128/78 mmHg HR: 77 bpm SpO_2: 96%	NE 0.05 mcg/kg/min	CI: 3.5 L/min/m^2 SVRI: 2325 dyn*s*cm^{-5}*m^2 GEDI: 783 mL/m^2 EVLWI: 9 mL/kg	CPK: 204 UI/mL Myoglobin: 44 ng/mL Hs-cTn: 95.5 ng/L NT-proBNP: 6514 pg/mL
ICU 72 h	BP: 118/74 mmHg HR: 75 bpm SpO_2: 98%			CPK: 99 UI/L Myoglobin: 35 ng/mL Hs-cTn: 54.49 ng/L NT-proBNP: 3919 pg/mL

BP Blood pressure, *HR* Heart rate, *CI* Cardiac index, *GEDI* Global and end diastolic index, *SVRI* Systemic vascular resistance index, *ELWI* Extravascular lung water index, *Hs-cTn* High-sensitivity cardiac troponin, *NT-proBNP* N-terminal-pro B-type natriuretic peptide

Given these results, the patient was transported to the catheterization laboratory for an acute coronary angiography, which revealed normal coronary arteries. A transthoracic echocardiogram was performed that showed a left ventricular dysfunction with a left ventricular ejection fraction of 35% and left ventricular basal hypokinesis.

A head computed tomography (CT) without contrast enhancement was performed showing diffuse subarachnoid haemorrhage extending into the ventricular system. There were no signs of cerebral oedema and no midline shift. In the CT angiography, an aneurysm in the left mid-cerebral artery was found.

Digital subtraction angiography remains the gold standard test for detecting intracranial aneurysms. It was performed just before the endovascular treatment.

43.3 Differential Diagnosis

First, clinicians should approach this case with a deep investigation related to the aetiology of coma. We should ask the family about any complain moments before the loss of consciousness. Moreover, we should check glucose levels, metabolic causes (liver failure, urea, and hypercapnia) and common drugs or toxic substance (benzodiazepines use, heroin or other central brain depressors drugs). Temperature impairments could affect awaking state such as serotonin syndrome, heat illness, or sepsis (last one specially in elderly people). Once all this had been dismissed, we should expand our investigations, and it is suggested to perform a brain CT or magnetic resonance to look for acute structural causes (ischaemic or haemorrhagic stroke).

In this case, the patient presented with chest pain and headache before the sudden loss of consciousness. Aneurysmal SAH should be the primary consideration when a patient presents with an abrupt headache with or without neurologic deficit, but there are many other causes of thunderclap headache such as acute hypertensive crisis, ischaemic stroke, or cerebral venous thrombosis that we should think about.

In our patient, the combination of chest pain and other cardiac manifestations together with the haemodynamic instability made us look for other causes before doing the brain CT. Potential life-threatening conditions should be ruled out; given its prevalence, acute myocardial ischaemia should be the first one; then we should also consider aortic dissection, myocarditis, or stress cardiomyopathy as well as some noncardiac causes.

43.4 Treatment

The patient was treated according to the current practice guidelines [3]. We prescribed a calcium channel blocker (nimodipine 60 mg/kg/4 h for 21 days) and an antiepileptic (Levetiracetam 500 mg i.v. /12 h for 5 days), which may be considered according to the AHA guideline 2012.

Analgosedation: continuous propofol (0.5–1.5 mg/kg/h) and fentanyl (0.5 mg/kg/h) perfusion for 5 days.

Inotropic drugs: Norepinephrine (0.3–0.8 mcg/kg/min) for 3 days and dobutamine 5mcg/kg/min for 12 h.

Endovascular coiling of the ruptured aneurysm was performed on the second day.

43.5 Evolution, Outcome, and Follow-Up

At ICU admission, her BP was 120/73 mm Hg on norepinephrine 0.8 mcg/kg/min, and her HR was 75 bpm. Volume-controlled ventilation was set to tidal volume of 480 mL, 13 breaths per minute, positive end-expiratory pressure (PEEP) of 5 cm H_2O, and fraction of inspired oxygen (FiO_2) of 30%. General measures were adopted according to the current guidelines [3]: upper body elevation with axially correct head positioning, semirecumbent position, analgesia, and sedatives.

A continuous haemodynamic monitoring device based on transpulmonary thermodilution was used to monitor the haemodynamic instability. First values were compatible with cardiogenic shock (Table 43.1). More fluids were administered, and an infusion of dobutamine was initiated at 5 mcg/kg/min.

The following 12 h in ICU were defined by the improving cardiovascular dysfunction making it possible to stop the dobutamine perfusion and drop the noradrenaline perfusion to 0.5 (Table 43.1). However, her gas exchange deteriorated, and FiO_2 and PEEP were increased to 50% and 8 cmH_2O, respectively. Chest X-rays showed signs of bilateral interstitial oedema, and lung ultrasound revealed multiple B lines bilaterally. A negative fluid balance was set including fluid restriction and furosemide 20 mg every 8 h.

The patient was transferred to the Radiology Department in the first 32 h, and the aneurysm was treated with endovascular coiling. There were no peri-procedural complications or postoperative vasospasm. After the procedure, the patient came back to the ICU.

At 48 h, ECG showed less profound T-waves in the precordial leads. Echocardiography revealed an improvement in the LVEF to 50%, and cardiac markers were normalizing (Table 43.1). Haemodynamic monitoring parameters were normal, and the device was withdrawn. The norepinephrine infusion was stopped on the third day. ECG and echocardiography completely normalized on the fourth day. Laboratory test still showed a high NT-proBNP, so maintenance fluids were stopped (Table 43.1).

Sedation was completely stopped on day 5. Health-care professionals observed an enhancement in the neurological examination (Glasgow Coma Scale, 10: O4V1M5), no response to orders, and noneye contact with isochoric and reactive pupils. CT scan revealed no signs of intracranial blood. Patient was extubated on day 10, still a bit bradypsychic and drowsy but without a focal neurological deficit. On day 14, patient was transferred to the neurosurgical ward.

43.6 Discussion

Cardiac complications after subarachnoid haemorrhage have an incidence around 15%–35% [2]; they vary from arrhythmias, alterations in contractility, or elevated cardiac enzymes to cardiac failure or cardiorespiratory arrest. Its pathophysiology is not completely known, and several mechanisms have been proposed, the most widespread being the stimulation of the hypothalamo-pituitary axis after haemorrhage that will cause a centrally mediated release of catecholamines within the myocardium.

Electrocardiographic abnormalities are the most common; they are found within the first 48–72 h. We can find from sinus bradycardia to ventricular arrhythmias and from T-wave alterations to ST-segment changes. Several studies have linked these changes in the ST segment and/or the T wave with a higher rate of complications such as delayed cerebral ischemia (DCI) and an increase in mortality [4].

Elevation of cardiac enzymes occurs in 20%–40% of patients [4]. Multiple studies had found an association between an increase in troponin levels and DCI, a worse prognosis, and an increase in mortality.

Echocardiographic abnormalities are various and sometimes are associated with decreased cardiac output. We can find both global and segmental wall motion abnormalities and systolic or diastolic dysfunction of the left ventricle. Acute left ventricular systolic dysfunction occurs in up to 30% of patients, and it has been referred to as neurogenic stress cardiomyopathy or neurogenic stunned myocardium (NSM). It usually develops within the first 2 days after the initial bleeding, and the timing of recovery ranges from a few days to weeks. Clinical management of patients with NSM is generally supportive; in case of cardiogenic shock, it should be treated with standard therapies including inotropes [5].

Pulmonary oedema is the most common pulmonary complication with an incidence ranging from 8% to 23% depending on the series. Neurogenic pulmonary oedema has a multifactorial origin but is mainly due to the effects of sympathetic discharge after the bleeding. Vasoconstriction increases pulmonary capillary pressure and consequently increases pulmonary capillary permeability. Nevertheless, pulmonary oedema may also be caused by cardiac dysfunction or be a side effect of fluid administration [6].

Recognizing the presence of myocardial dysfunction is paramount in the critical care management of aneurysmal SAH patients as it influences the outcome. This is usually accomplished with ECG, echocardiography, and cardiac enzyme monitoring. Since the dysfunction is reversible, early recognition will help to differentiate from acute coronary syndrome and prevent unnecessary further tests. It is also important to assess the severity of myocardial dysfunction and adjust the treatment accordingly. In the presence of myocardial dysfunction or pulmonary oedema, it will be important to use intravenous fluids and inotropes judiciously.

Take-Home Messages

- Sudden-onset severe headache with or without a neurologic deficit needs immediate evaluation for subarachnoid haemorrhage.
- Electrocardiographic changes, regional wall motion abnormalities, and elevation of cardiac enzymes related to acute brain injury should make you think of neurogenic stunned myocardium.
- Clinical management of patients with neurogenic stunned myocardium is generally supportive because the cardiac abnormalities usually normalize spontaneously within a few days to weeks.

Summary

A 56-year-old female was brought to our emergency department (ED) after loss of consciousness at home preceded by chest pain and headache. In the ED, she showed the whole spectrum of neurocardiogenic effects in subarachnoid haemorrhage: electrocardiographic changes, regional wall motion abnormalities, and elevation of cardiac enzymes. Coronary angiography revealed normal coronary arteries. Echocardiography showed left ventricular basal hypokinesis and left ventricular dysfunction. Subsequently, cerebral computed tomography revealed diffuse subarachnoid haemorrhage due to a ruptured intracranial aneurysm. After her admission in the ICU, she developed cardiogenic shock and pulmonary oedema. Her aneurysm was obliterated with endovascular treatment. There were no intracranial complications, and the cardiovascular abnormalities resolved during her stay in the ICU. At discharge, both the echocardiography and the electrocardiogram were normal.

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Principles and Management of Severe Trauma and Bleeding

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Contents

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Learning Objectives

- Describe a structured assessment of the trauma patient.
- Recognize the importance of performing a proper primary survey.
- Summarize specific guidelines for bleeding trauma patients.
- List the different components of the secondary survey.

44.1 Introduction

Severe trauma is a major global health problem and one of the leading causes of death among young people. Trauma is still the leading cause of death for people under the age of 40, although mortality rates vary widely between countries [1]. Severe trauma is mainly caused by road traffic injuries, falls and assaults. According to the most recent report from the World Health Organization (WHO), there were 1.35 million road traffic deaths globally in 2018, with millions more sustaining serious injuries and living with long-term adverse health consequences [2]. Road traffic injuries are currently estimated to be the eighth leading cause of death across all age groups globally.

Severe trauma is a time-dependent disease. Mortality follows a trimodal distribution [3]:

- First peak or immediate deaths. Deaths in the first seconds or minutes of injury, as a result of rupture of the heart, aorta, or other large blood vessels, or apnoea due to severe brain or high spinal cord injury. Prevention is the only way to reduce these.
- Second peak or early deaths. Deaths within minutes or hours after injury, caused by major cardiovascular injuries, severe abdominal lesions, pelvic fractures with subsequent exsanguination or major intracranial bleeding. This is the most crucial period, with the speed and quality of trauma care determining the patient's outcome. This period has been termed the 'golden hour'.
- Third peak or late deaths. Deaths after several days or weeks after the initial injury, secondary to complications such as sepsis or multiorgan dysfunction.

Care of the trauma patient must be coordinated, continuous and constantly reassessed. Physicians must rapidly evaluate the patient using a systematic approach and institute life-saving manoeuvres when necessary. The creation and adherence to local protocols should be promoted to reduce transfer times and improve the care of these patients, thus reducing their mortality and optimising the management of available resources.

Protocols for 'initial assessment' should include a series of well-defined but continuous phases. This approach includes primary and secondary surveys, which must be repeated frequently to identify any changes in the patient's condition that indicate the need for additional intervention.

44.2 Primary Survey

The primary survey is the initial assessment and management of a trauma patient. It is conducted to detect and treat actual or imminent life threats and prevent complications from these injuries. The leading causes of death in trauma patients are airway obstruction, respiratory failure, haemorrhagic shock, and brain injury. Therefore, these are the areas prioritised by the primary survey.

The most common acronym for performing the primary trauma survey is ABCDE, each letter representing an area of focus [4, 5]. If any abnormality is identified in one of the areas of focus, it should be intervened upon before a practitioner progresses further through the algorithm. In single responder settings, these may need to be addressed in a linear way; however, when a team is assembled, these elements may be addressed simultaneously. The exception to this approach is if a patient appears to be exsanguinating from a massive wound, this should be addressed before starting the ABCDE algorithm. The primary survey should be frequently repeated to identify any deterioration in the patient's status that indicates the need for further interventions.

ABCDE sequence (Table 44.1) [5]:
Airway maintenance with restriction of cervical spine movement
Breathing and ventilation
Circulation with haemorrhage control
Disability (neurological evaluation)
Exposure and environmental control

Table 44.1 ABCDE sequence. Adapted from Peran et al. [6]

	EXAMINATION	INTERVENTION	GOAL
A AIRWAYS	Voice See/ Listen/Feel Breathing sounds	Head tilt + chin lift Oxygen (15l/min) Succion	Patient airway
B BREATHING	Respiratory rate (12–20 min) Chest wall movements Chest percussion Lung auscultation Pulse oximetry (97%–100%)	Rescue breaths Bag-mask ventilation Inhaled medications Decompress tension pneumothorax	Sufficient Oxygenation and Ventilation
C CIRCULATION	Skin color, sweating Capillary refill time Palpate pulse rate + Heart auscultation Blood pressure Electrocardiography monitoring	Stop bleeding Intravenous access Infuse saline	Stabilization of circulation
D DISABILITY	Level of consciousness AVPU (Alert/ Voice responsive/ Pain responsive / Unresponsive) Limb movements Pupillary light reflexes Blood glucose	Treat Airway, Breathing, and Circulation problems Recovery position Glucose for hypoglycemia	Evaluate neurological state
E EXPOSURE	Expose skin Temperature	Treat suspected cause	Revealing other symptoms and thermo-management

44.2.1 A: Airway Maintenance with Restriction of Cervical Spine Movement

Airway obstruction is the leading cause of preventable death in these patients. Our first goal is to assess airway patency and stability and plan for advanced airway management if required. Frequent re-evaluation of airway patency is essential to identify and treat patients who are losing the ability to maintain a patent airway.

We must look for any sign of airway obstruction, partial or complete, and exclude inhaled foreign bodies, accumulated blood or secretions and any facial or neck injury that can lead to an obstructed airway. If the patient is able to communicate in a normal voice, their airway is patent. Patients with a reduced level of consciousness, Glasgow Coma Scale (GCS) score of 8 or lower, usually require establishing a definitive airway. Chin-lift and jaw-thrust manoeuvres are appropriate temporising measures.

During airway assessment and management, we should take care of the cervical spine, which may have been damaged. Usually, the cervical spine is protected with a cervical collar, although this practice is controversial particularly for patients with isolated penetrating traumatic injuries. However, if we need to manage the airway, a team member should manually restrict its motion with in-line stabilisation [7].

44.2.2 B: Breathing and Ventilation

The patency of the airway, by itself, does not ensure adequate oxygenation and ventilation. At this stage, we should administer oxygen to ensure adequate saturation and evaluate the patient for signs and symptoms that indicate a possible alteration of the lung, chest wall or diaphragm, through auscultation and palpation of the precordium. Percussion might be difficult in noisy environments.

The most serious lesions that compromise ventilation are massive haemothorax, tension pneumothorax and unstable chest with associated pulmonary contusion. These may also produce significant haemodynamic alterations. In cases of tension pneumothorax or massive haemothorax, a chest drain must be placed immediately in the 4th–5th intercostal space through the midaxillary line.

Other injuries such as fractured ribs, simple pneumothorax or pulmonary contusion are usually identified in the secondary survey given that they impair ventilation to a lesser degree.

44.2.3 C: Circulation with Haemorrhage Control

Bleeding and shock are important and preventable causes of death in trauma. We must evaluate for the presence of shock in our patients and determine its aetiology. There are initial signs and symptoms that should make us suspect a shock state: the level of consciousness, skin perfusion (paleness, coldness, capillary refill time >2 s) and the characteristics of central pulses. A 'Shock Index' (Heart rate/Systolic Blood Pressure) ≥1 may be a good predictor of massive haemorrhage and can be consid-

ered along with the clinical history and other examination findings suggestive of a shock state [8, 9].

Once shock has been identified, the type of trauma and its biomechanics will allow us to determine its cause: hypovolemic (haemorrhage), obstructive (tension pneumothorax or tamponade), cardiogenic (myocardial contusion) and neurogenic (spinal cord injury). We should also keep in mind the possibility that the patient may have more than one type of shock.

By far, the most common cause of shock in these patients is bleeding. Once tension pneumothorax has been ruled out, hypotension is due to blood loss until proven otherwise.

44.2.3.1 Bleeding

Bleeding sources can be divided into two types: external and internal. Diagnosis of external bleeding is simple and should be controlled initially with direct manual compression of the wound and elevation of the limb with or without proximal compression if arterial bleeding is suspected. Tourniquet use can be considered for medical or tactical reasons such as uncontrollable limb bleeding, severe bleeding and simultaneous ABC problem, inaccessibility of the injured region (entrapment), 'care under fire' situation, patient number or injury severity exceeds rescuer capacity for other bleeding control technique [10].

Haemodynamically unstable internal haemorrhage is usually limited to five possible sites: chest, abdomen, pelvis, retroperitoneum and long bones. The initial physical examination should alert us to the likely bleeding site: hypoventilation related to a haemothorax, a distended abdomen, instability of the pelvic ring or increase in the diameter of a limb. To aid diagnosis, we can also use imaging at the bedside such as chest X-rays, pelvic X-rays or thoracic and abdominal ultrasound. Initial management may include chest decompression, application of a pelvic-stabilising device or extremity splints.

Bleeding patients will exhibit a number of clinical signs derived from the physiologic effects of the haemorrhage. The ATLS (advanced trauma life support) guidelines classify haemorrhagic shock into four grades based on clinical and biochemical abnormalities (◘ Table 44.2). This classification system is useful in the early stage to guide initial therapy [5].

Definitive bleeding control, being surgical or interventional radiological treatment, is paramount together with volume resuscitation [11]. Vascular access must be established as soon as possible, commonly two large-bore peripheral catheters. If this is not immediately possible, central venous lines or intraosseous access may be used. Fluid therapy with crystalloids, preferably balanced solutions, should be initiated, although to minimise exacerbation of bleeding, permissive hypotension is advised. A target mean arterial pressure of 50–60 mmHg is recommended; however, if severe traumatic brain injury is suspected, a higher target of 80 mmHg is suggested [12, 13]. Fluids must be administered judiciously, as aggressive resuscitation before control of bleeding has been demonstrated to increase morbidity and mortality. If the patient is not fluid responsive, vasopressors should be initiated together with an inotropic agent if myocardial dysfunction is evident.

Table 44.2 Classification of haemorrhagic shock. Adapted from ATLS [5]

	Class I	Class II (MILD)	Class III (moderate)	Class IV (severe)
Blood loss (approximate)	<15%	15–30%	31–40%	>40%
Heart rate	≈	≈/↑	↑	↑/↑↑
Pulse pressure	≈	↓	↓	↓
Blood pressure	≈	≈	≈/↓	↓
Respiratory rate	≈	≈	≈/↑	↑
Urine output	≈	≈	↓	↓↓
GCS[a]	≈	≈	↓	↓
Base déficit[b]	0 to −2 mEq/L	−2 to −6 mEq/L	−6 to −10 mEq/L	−10 or less mEq/L
Need for blood products	Monitor	Possible	Needed	Massive transfusion protocol

[a]Glasgow Coma Scale
[b]Base déficit indicates metabolic acidosis, is the quantiti of base (HCO_3- in mEq/L) that is below normal range

In severe trauma patients, coagulopathy is frequently observed in the acute phase. This coagulopathy is caused by multiple factors associated with the trauma itself as well as certain interventions, like resuscitative measures. Trauma-induced coagulopathy (TIC) describes abnormal coagulation processes that are attributable to trauma. In the early hours, hypocoagulability is typically present, resulting in bleeding, whereas later, we may find a hypercoagulable state associated with venous thromboembolism and multiple organ failure. Several pathophysiological mechanisms underlie TIC. Tissue injury and shock synergistically provoke endothelial, immune system, platelet and clotting activation, which are accentuated by the 'lethal triad' of coagulopathy, hypothermia and acidosis [14]. Management priorities are stopping blood loss and reversing shock by restoring circulating blood volume, to prevent or reduce the risk of worsening TIC.

The hospital's massive transfusion protocol should be activated if severe bleeding or haemorrhagic shock is suspected. At baseline, blood components are administered at a predefined low ratio, 1:2 or 1:1 of red blood cells and fresh frozen plasma. Platelets should also be transfused. Subsequently, we can guide our resuscitation with coagulation or viscoelastic tests. Tranexamic acid must be administered in the first 3 h after the injury at a loading dose of 1 g infused over 10 min, followed by an infusion of 1 g over 8 h [11].

44.2.4 D: Disability (Neurologic Evaluation)

Neurological examination will include assessment of level of consciousness using the Glasgow Coma Scale, size, symmetry and pupil reactivity, search for signs of focal neurological involvement (presence of lateralising signs) and determination of level of spinal cord injury, if any.

If there is suspicion of neurological trauma, we must adapt the resuscitation measures mentioned above to obtain an adequate cerebral and/or spinal cord perfusion pressure and minimise secondary injury. Likewise, if there is a suspicion of increased intracranial pressure (ICP), evidenced by pupil alterations (anisocoria, bilateral mydriasis), we should initiate osmotherapy treatment with mannitol or hypertonic saline, preferably with hypertonic solutions if the patient is shocked. We should also implement other measures that help reduce ICP (sedation and analgesia, optimal oxygenation and ventilation; optimise patient position with head up to 30–45 degrees if possible, etc.) [15].

44.2.5 E: Exposure

Complete exposure of the patient will help facilitate a thorough examination and assessment. Once completed, the patient should be covered with blankets to prevent hypothermia. Hypothermia may be present on admission, so the trauma resuscitation area should have a warm ambient temperature and we should aggressively treat hypothermia with warm fluids and blankets.

Together with this primary survey, we should also continuously monitor pulse oximetry, end-tidal carbon dioxide and electrocardiography. Extract blood samples for transfusion cross-matching, biochemistry and haematology tests as well as arterial blood gases. Request urgent chest and pelvis X-rays, and place urinary and gastric catheters if needed.

44.3 Secondary Survey

The secondary survey is performed once the patient has been resuscitated and stabilised [16]. It involves a more thorough head-to-toe examination, and the aim is to detect other significant but not immediately life-threatening injuries (Table 44.3). At any point in the care of a trauma patient where any deterioration is detected, we must go back and reassess the primary survey.

The secondary survey should also include taking a history of the mechanism of injury. The patient's condition is greatly influenced by the mechanism of injury, and some injuries can be predicted based on the direction and amount of energy involved. We can collect vital information using the AMPLE mnemonic: allergies, medication, past illness/pregnancy, last meal and events/environment related to the injury [5]. At this stage, we should also request any additional tests to identify specific injuries, such as computerised tomography or ultrasound.

Table 44.3 Secondary survey. Adapted from ATLS [17]

Secondary survey			
Item to assess	**How to asses**	**Identifies/findings**	**Confirmation**
Level of consciousness	Glasgow Coma Scale (GCS)	Severity of head injury: GCS 13–15, minor head injury GCS 9–12, moderate head injury GCS <8, severe head injury	CT scan Repeat if paralysing agents (without them)
Pupils	Size Shape Reactivity to light	Type of head injury: – mass effect – diffuse brain injury Ophthalmic injury	CT scan
Head	Palpable defects Inspect for lacerations/fractures	Scalp laceration Depressed or basilar skull fractures	CT scan
Maxillofacial	Deformity Malocclusion Crepitation	Injury from: – bone – soft tissue – nerve – teeth/mouth	X-ray CT scan
Neck	Visual Palpation Auscultation	Neck injury or neurologic deficit – deformity – emphysema – hematoma – bruit – platismal penetration – pain	X-ray CT scan Angiography Esophago-/laryngoscopy
Thorax	Visual Palpation Auscultation	Thoracic wall injury Haemo-/pneumothorax Bronchial injury Contusion Aortic disruption Findings: – Bruising, deformity or paradoxical motion – Chest-wall tenderness, crepitation – Diminished breath sounds – Muffled heart tones – Mediastinal crepitation – Severe back pain	X-ray CT scan Angiography Bronchoscopy Tube thoracostomy Pericardiocentesis Transesophageal echocardiogram
Abdomen	Visual Palpation Auscultation	Abdominal Intra-/retroperitoneal injuries – Pain/tenderness – Peritoneal irritation – Visceral/retroperitoneal organ injury	CT scan X-ray Angiography Diagnostic Peritoneal Lavage Abdominal ultrasound Laparotomy

Table 44.3 (continued)

Secondary survey			
Item to assess	**How to asses**	**Identifies/findings**	**Confirmation**
Pelvis	Palpate symphysis pubis for widening Palpate for tenderness Determine pelvic stability only once Inspect perineum Rectal/vaginal exam	Genitourinary tract injuries Pelvic fractures – Haematuria – pelvic fracture – rectal, vaginal, and/or perineal injury	X-ray Genitourinary contrast studies Urethrogram Cystogram CT scan
Spinal cord	Motor and pain response	Cranial, cord, peripheral nerves injuries – quadriplegia – paraplegia – unilateral mass effect – nerve root injury	X-ray CT scan MRI
Vertebral column	Response to pain Palpate Deformity	Column, vertebral and nerve injuries – fracture – dislocation	X-ray CT scan MRI
Extremities	Visual inspection Palpation	Soft tissue, bone, joint and neurovascular injuries – Pain, crepitation, tenderness – swelling, bruising, pallor – malalignment – absent/diminished pulses – tense muscular compartments – neurologic deficits	X-ray Doppler examination Compartment pressures Angiography

Take-Home Messages

- Severe trauma is a time-dependent disease that requires a coordinated response in which the speed and quality of our actions save lives.
- In the primary survey, it is very important to follow the ABCDE approach, except in exsanguinating wounds.
- The resuscitation of these patients must be based on permissive hypotension, moderate crystalloid infusion, massive transfusion protocols and control of the factors of the 'lethal triad'.
- The secondary survey involves a head-to-toe examination, where the aim is to detect significant but not immediately life-threatening injuries.
- At any point in the care of a trauma patient where any deterioration is detected, we must go back and reassess the primary survey.

Summary

Severe trauma is one of the leading causes of death among young people. Treatment of these patients requires a rapid assessment of injuries and institution of life-preserving therapy. Timing is crucial in trauma, so a systematic approach that can be rapidly and accurately applied is essential. The primary survey is conducted to detect and treat actual or imminent life threats and prevent complications from these injuries. The most common acronym for performing the primary trauma survey is ABCDE. Once the patient has been resuscitated and stabilised, the secondary survey is performed, which involves a more thorough examination and a complete history. The primary and secondary surveys should be repeated frequently to identify any change in the patient's status that indicates the need for additional intervention.

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Continuous Renal Replacement Therapy Management in a Patient with Severe Traumatic Brain Injury and Rhabdomyolysis-Associated Acute Kidney Injury

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Contents

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Learning Objectives

- Advantage and disadvantage of continuous renal replacement therapy
- Management of renal replacement therapy in case of traumatic brain injury
- Management of renal replacement therapy for rhabdomyolysis-associated acute kidney injury using different membranes and modalities
- The risk/benefit ratio in using anticoagulation strategies for continuous extracorporeal circuits in patients with traumatic brain injury

45

45.1 Introduction

Historically, acute kidney injury (AKI) has been considered a rare complication in traumatic brain injury (TBI) patients, with the majority of cases occurring in the setting of multiple-organ trauma with muscle injury or multiple-organ failure. Recently, AKI has been reported to affect from 8% to 20% of TBI patients and has been associated with poor prognosis [1, 2]. In a TBI patient with rhabdomyolysis-associated AKI, reducing renal injury from myoglobin and other nephrotoxins may be crucial to increase the probability to survive. So far, although the rationale for a quick and effective removal of myoglobin in acute rhabdomyolysis would be strong and logical, the practical results with conventional therapies have been proven to be modestly useful [3]. Nowadays, we may reconsider the extracorporeal removal of myoglobin by using innovative membranes like high cutoff membranes. The high-flux membranes are characterized by a high permeability of middle-large molecules during convection. Conversely, high cutoff membranes are identified by an increased pore size distribution, which allows the removal of middle-large molecules during diffusion. Despite the accepted use of continuous renal replacement therapy (CRRT) in patients with traumatic brain injury (TBI) and coexisting AKI, there is still limited data on safety and no data regarding the timing and optimal modality of CRRT. Particularly, there is still controversy concerning the advantage of hemofiltration versus hemodialysis over the other in the setting of AKI. For this reason, the use of CRRT for rhabdomyolysis-associated AKI in severe trauma patients with severe TBI could be really challenging. We report a therapeutic approach in a trauma patient with severe TBI for extracorporeal removal of myoglobin in rhabdomyolysis-associated AKI, exploring trends in cerebral hemodynamics, solute concentrations, and osmolarity.

Case Study

We present the case of a 55-year-old male, with a medical history of obesity (body mass index = 37) and diabetes mellitus, who experienced blunt trauma due to car-pedestrian traffic accident. He was found unconscious, gasping, with a Glasgow Coma Scale score of 7, which required intubation in situ and transfer to our Trauma Center Department (Level I) by an ambulance.

At the time of arrival to the shock trauma room, his primary survey revealed a patient intubated with c-spine control, tachypneic at 30 breaths/min, saturating 80%–85% with 100% fractional inspired oxygen, profound hemodynamic instability, with a blood pressure of 65/45 mmHg, and a heart rate of 145 bmp. The Glasgow Coma Scale score was 3, with normal pupils' size and reactivity.

Within the first hours, according to Brain Trauma Foundation guidelines [4], he received standard ICU care (vital signs monitoring, central venous pressure monitoring via a central venous line, nasogastric tube, hourly diuresis monitoring). He received analgesia and sedation with fentanyl and propofol (Richmond Agitation Sedation Scale, -4) and was mechanically ventilated in volume control. The ventilator parameters were set to maintain the partial pressure of carbon dioxide in arterial blood ($paCO^2$) between 30 and 35 mmHg (mild hyperventilation). The head of the bed was raised at 45 degrees. Mannitol therapy was prescribed, and vasopressors were used to target cerebral perfusion pressure (CPP) at 50–70 mmHg. During the first 12 h, intracranial pressure (ICP) ranged from 17 to 26 mmHg, responsive to bolus of intravenous mannitol, with a mean CPP of 53 ± 17.55 mmHg with a vasoactive inotropic score of 73 ± 3.5. The mean $paCO^2$ was 38 ± 13.5 mmHg, and the paO^2 (partial pressure of oxygen in arterial blood)/FiO^2 (fraction of inspired oxygen) ratio was 90 ± 29.4 mmHg. A diclofenac infusion was necessary to control the temperature, while other pharmacological and physical measures weren't effective.

Within 12 h of admission, the patient became oliguric (0.4 mL/kg/h) with a fluid overload of 5%, due to aggressive fluid resuscitation and a rise in serum creatinine (sCr) more than 1.5 times the admission value.

45.2 Investigations

A focused assessment with sonography for trauma showed no lung sliding in the right lung, and a thoracic drainage was placed. No other sonographic abnormalities were found. After resuscitation and supportive therapy, the patient underwent intravenous contrast computerized tomography (CT) scan, which revealed subarachnoid hematic suffusion, contusion of the temporal right lobe, multiple skull fractures, and unstable cervical fractures. As summarized in Table 45.1, the estimated Injury Severity Scale score was 43, and the estimated New Injury Severity Scale score was 43. A second CT of the brain was performed and showed increased subarachnoid hemorrhage and interhemispheric acute subdural hematoma but also a very small left subdural hematoma without mass effect. In addition, magnetic resonance imag-

Table 45.1 Injury Severity Scale score

Region	Injury description	AIS	Square top three
Head and neck	Subarachnoid hematic suffusion Interpedicular and prepontine cistern hematic suffusion Contusion of the temporal right lobe Frontal and parietal fractures Left occipital fracture C2 body and odontoid fractures Left posterior tubercle of C6	3 2 3 2 3 3 2	9
Face	No injury	0	
Chest	Fracture diastase of soma T4 Vertebral fractures T1-T3-T4-T5-T6-T7-T8 Fracture displaced to the middle III of the T4 soma, extended to the spinous process Bilateral hemothorax Bilateral pulmonary contusions Pneumomediastinum Displaced fracture of the sternal handlebar Decomposed fracture of the right clavicle, dislocation of the left acromion-clavicular and sternoclavicular joints Thickening of the left small pectoral muscle Compound fracture of the posterior arch of the II rib, bilaterally, and of the left posterior arch of the III and IV coast	2 2 2 2 3 3 2 2 2 3	9
Abdomen	Retroperitoneal hematoma Left psoas muscle contusion	2 1	
Extremity	Multiline fracture of the right scapula Displaced fracture of the left acromial process Fracture composed of the left scapular body Multiple pelvic fractures Displaced pluriframmentary fracture of the left shaft of tibia and fibula and distal third	2 2 2 5 2	25
External	No injury	0	
Injury severity score			43

Abbreviations: *AIS* Abbreviated injury scale

ing of the spinal cord was requested by the neurosurgeon and was performed before the placement of invasive monitoring of intracranial pressure (ICP). The first ICP measurement was 8 mmHg. Laboratory results reported high level of white blood cells and procalcitonin ($14.1*10^3$/μL and 55.45 ng/mL, respectively) as well as increased serum creatinine phosphokinase and myoglobin (40,724 U/L and 73,873 μg/L, respectively).

45.3 Treatment

Based on the ability of continuous forms of renal replacement therapy to provide an effective therapy in terms of solute clearance, coupled with improved cardiovascular and intracranial stability, and based on the capacity of high cut-off (HCO) filter to allow rapid and effective removal of myoglobin and cytokines from the circulation, in agreement with nephrologist, we initiated at 16 hours post-injury a treatment with continuous veno-venous hemodialysis (CVVHD) modality (Qb 220 mL/min, Qd 3,500 mL/h, Quf 50 mL/h) with a dialytic dose of 35 mL/kg/h using a high cutoff (HCO) filter (Theralite®, Baxter, 2.1 m^2). This prescription was alternated to high-volume hemofiltration (HVHF) modality (Qb 220 mL/min, Qrpre 3,000 mL/h Qrpost 1,000 mL/h, Quf 50 mL/h) with a dialytic dose of 55 mL/kg/h and high-flux polysulfone filter (AV1000S®, Fresenius, 1.8 m^2). Considering the effects of systemic anticoagulants on intracerebral hemorrhage, either at the site of damage or around the intracranial pressure monitoring device, no anticoagulation strategy was preferred for the first 24 h. Then, anticoagulation with a low dose of heparin (pre-hemofilter low-molecular-weight heparin 2,000 IU twice a day) was initiated, and the patient did not experience any thrombotic/hemorrhagic events. Table 45.2 sum-

Table 45.2 Laboratory values and cerebral hemodynamics parameters

	Pre-CRRT	HCO-CVVHD	HF-HVHF	Post-CRRT
Blood chemistry				
Myoglobin (μg/L)	73,873	21161[a]	12169[a]	1686
Sodium (mmol/L)	147.7 ± 6.9	143.5 ± 3.5	139.0	144
Urea (mg/dL)	16.5 ± 5.1	22.5 ± 2.1	17	61
Osmolarity (mOsm/L)	324 ± 12.0	314 ± 7.1	299	325
Arterial blood gases				
Bicarbonate (mmol/L)	21.4 ± 3.3	21.1 ± 2.5	24.7 ± 0.8	24.3 ± 0.7
pCO2 (mmHg)	46.5 ± 14.6	39 ± 2.8	41 ± 3.5	31 ± 5
paO_2/FiO_2	90 ± 36.0	115 ± 36.8	92 ± 19.0	268 ± 12.7
Hemodynamic parameters				
ICP (mmHg)	21.7 ± 3.8	17.4 ± 3.3	19.8 ± 2.7	14.0 ± 3.0
MAP (mmHg)	81 ± 18.0	72.5 ± 9.5	89.1 ± 7.5	80.3 ± 13.1
CPP (mmHg)	58.33 ± 21.5	54.36 ± 7.03	69.36 ± 7.78	66.4 ± 14.4
VIS	73 ± 4.35	93 ± 17.82	78 ± 36.41	0

Abbreviations: *ICP* intracranial pressure, *MAP* mean arterial pressure, *CPP* cerebral perfusion pressure, *VIS* vasoactive inotropic score
HCO-CVVHD and HF-HVHF data refer to values collected during the first 24 h of each treatment
[a]Myoglobin levels at the end of 24 h of treatment

marizes changes in laboratory values and cerebral hemodynamics related to CRRT. HCO-CVVHD allowed a rapid removal of myoglobin (21,161 μg/L after 16 h of treatment), while a slower and stable decrease was registered during HF-HVHF (12,169 μ/L after 24 h of treatment).

45.4 Evolution, Outcome, and Follow-Up

A total renal replacement therapy of 48 h was considerable for crush syndrome improvement and hemodynamic stability, in terms of mean arterial pressure, cerebral perfusion pressure, and vasoactive inotropic score. A target $PaCO_2$ of 35–38 mmHg was reached, and PaO_2/FiO_2 ratio upgraded after 2 days of treatment. The weaning from CRRT was effective after a total of 96 h of treatment. Renal function recovered completely to baseline sCr at time of ICU discharge. Due to severity of cervical lesions, the patient was paraplegic and transferred to a rehabilitation.

45.5 Discussion

Based on the Kidney Disease: Improving Global Outcomes (KDIGO) Guidelines, the use of CRRT over intermittent therapies in TBI patients with coexisting AKI should be preferred [5]. The "urea reversal effect" and impact on hemodynamics were indicated as causes of ICP elevation during intermittent treatment. In the present case report, hypovolemia and hypermyoglobinemia have been considered the major determinants for AKI initiation, even if several factors might have perpetuated the renal insult in the following days: unstable hemodynamics, reduced oxygenation, nephrotoxic exposure (contrast medium and mannitol), neuroinflammation, and also sepsis. AKI syndrome can develop as a consequence of different pathological conditions that can interfere with a combined causality depending on the intensity of the exposure. TBI could have triggered a complex cascade of molecular and cellular events mediated by cytokines and chemokines, which have been associated with distant organ failure and acute tubular injury. CRRT is a dialysis modality that offers multiple advantages for patients who are critically ill with acute kidney injury (AKI) in the intensive care unit (ICU): solute management, acid-base stability, and volume control. The development of new membranes, such as HCO membranes, enables the removal of middle-large substances by convective and/or dialytic CRRT modalities. Although with limited evidence, the HF membranes coupled with the high convective dose of HVHF are able to increase the passage of middle-large solutes. The concentration gradient between blood and dialysate during CVVHD modality may instead be used with HCO filters, taking advantage from the elevated pore size to enable the passage of middle-large molecules. The customized prescription of different CRRT modalities with these innovative membranes allowed a quick removal of myoglobin, favoring a rapid recovery of renal function. Our CRRT prescription also allowed cytokine removal limiting neuroinflammation, with improvement of hemodynamics and respiratory changes. However, continuous extracorporeal circuits required an anticoagulation strategy, and patients with TBI with or without invasive intracranial devices are at increased risk of intracranial hemorrhage. In fact, the

injured brain triggers multiple, highly complex, interactive pathways that can result in hemostatic failure and hemorrhagic progression. On the other hand, a hypercoagulable state has been observed even days after the primary insult. High-quality data on optimal approach and the timing of initiation of thromboprophylaxis are lacking, and the current literature [6] suggests an individualized approach, based on a careful evaluation of risk factors. KDIGO guidelines strongly recommend the use of an anticoagulation strategy [5] with regional citrate anticoagulation during CRRT. In our patient, regional citrate anticoagulation was not used because of increased risk of citrate accumulation during regional citrate anticoagulation and a free-anticoagulant first and a low-dose heparin treatment then was preferred. Even though our patient did not experience any episodes of thrombosis or hemorrhage after initiation of CRRT, the risk/benefit ratio should be balanced case-by-case.

Take-Home Messages

- Continuous renal replacement therapy offers hemodynamic stability and slow but prolonged solute clearance.
- In patients with traumatic brain injury and coexisting acute kidney injury requiring renal support, continuous renal replacement therapy should be preferred to avoid rapid changes in intracranial pressure.
- In rhabdomyolysis-associated acute kidney injury, the use of high cutoff membrane coupled with continuous veno-venous hemodialysis or high-flux hemofiltration allows quick removal of myoglobin, favoring a rapid recovery of renal function.
- Continuous extracorporeal circuits require an anticoagulation strategy and patients with TBI with or without invasive intracranial devices are at increased risk of intracranial hemorrhage. The risk/benefit ratio should be balanced case-by-case.

1. Why is it preferrable to use a continuous renal replacement therapy in case of traumatic brain injury with acute kidney injury?
2. What is the rationale to use a high cutoff membrane to remove myoglobin?
3. What is the rationale to use high-volume hemofiltration to remove myoglobin?
4. Is it necessary to prescribe an anticoagulation strategy for continuous renal replacement therapy?

1. Because continuous modalities offer hemodynamic stability and avoid the "urea reversal effect," limiting the effect on cerebral dynamics.
2. High cutoff membrane enables the removal of middle-large substances by convective and/or dialytic CRRT modalities.
3. High-flux membranes used in combination with a high convective dose are able to increase the passage of middle-large solutes.
4. Yes, anticoagulation strategy is a fundamental part of CRRT prescription. Based on patient's clinical status, clinicians can decide to use regional citrate anticoagulation (as recommended by KDIGO guidelines), systemic heparin anticoagulation, or no anticoagulation.

Summary

Introduction. Acute kidney injury (AKI) may result after multiple trauma injury and is associated with poor prognosis. The use of renal replacement therapy in traumatic brain injury (TBI) patients may be challenging. We report a therapeutic approach in a trauma patient with severe TBI for extracorporeal removal of myoglobin in rhabdomyolysis-associated AKI.

Case Presentation. A 55-year-old male was admitted in intensive care unit (ICU) for multiple trauma and severe TBI, complicated by hemorrhagic shock, acute respiratory distress syndrome, sepsis, and rhabdomyolysis-associated severe AKI. Based on the ability of continuous forms of renal replacement therapy to provide an effective therapy in terms of solute clearance, coupled with improved cardiovascular and intracranial stability, an alternation of a high cut-off continuous veno-venous hemodialysis (HCO-CVVHD) and a high-flux high-volume hemofiltration (HF-HVHF) modalities was prescribed. A free-anticoagulation strategy was preferred during the first 24 h, followed by a low-molecular-weight heparin treatment and the patient didn't experience any episodes of hemorrhage or thrombosis. A total renal replacement therapy of 48 h was considerable for crush syndrome improvement and hemodynamic stability, in terms of mean arterial pressure and cerebral perfusion pressure. The weaning from renal replacement therapy was effective after a total of 96 h of treatment. Renal function recovered completely to baseline serum creatinine at time of ICU discharge.

Conclusion. In a severe TBI patient with rhabdomyolysis-associated AKI, a slower but prolonged solute clearance, coupled with improved cardiovascular and intracranial stability, avoiding rapid changes in intracranial pressure, was performed customizing the prescription by alternating HCO-CVVDH with HF-HVHF.

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Delayed Post-Traumatic Tamponade: The End of the Tunnel

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Contents

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Learning Objectives

- Knowing the existence of delayed post-traumatic tamponade
- Knowing how to identify the differential diagnoses of a tamponade
- Knowing the anesthetic management of a tamponade
- Identify some interesting indications of gastric ultrasonography in anesthesia and intensive care
- Knowing the existence and the risks inherent to the fixation bias

46.1 Introduction

Cardiac tamponade is an alteration in the diastolic filling of the ventricles that results in a reduction of cardiac output, in the context of compression of the cardiac chambers by a pericardial effusion [1]. Traumatic myocardial contusion is a rare cause of cardiac tamponade, which is most often secondary to cardiac surgery or adjacent neoplasia.

The diagnosis of tamponade can be challenging because tachycardia, the most common sign, is also an unspecific sign. This is especially true when the compression of the chambers worsens in a slowly progressive manner, as the heart can tolerate pericardial effusion volumes of up to 2 L (Fig. 46.1) [1].

Once diagnosed, treatment is based on urgent percutaneous or surgical ventricular decompression. The anesthetic management of the surgical procedure is a critical step: One should avoid to increase the stress on the right ventricle when putting it on positive pressure ventilation, while limiting the risk of inhalation if a strategy of sedation with spontaneous ventilation is chosen.

We present here the case of a 28-year-old patient managed in the intensive care unit for a severe thoracic trauma by crushing in the context of a traffic road accident.

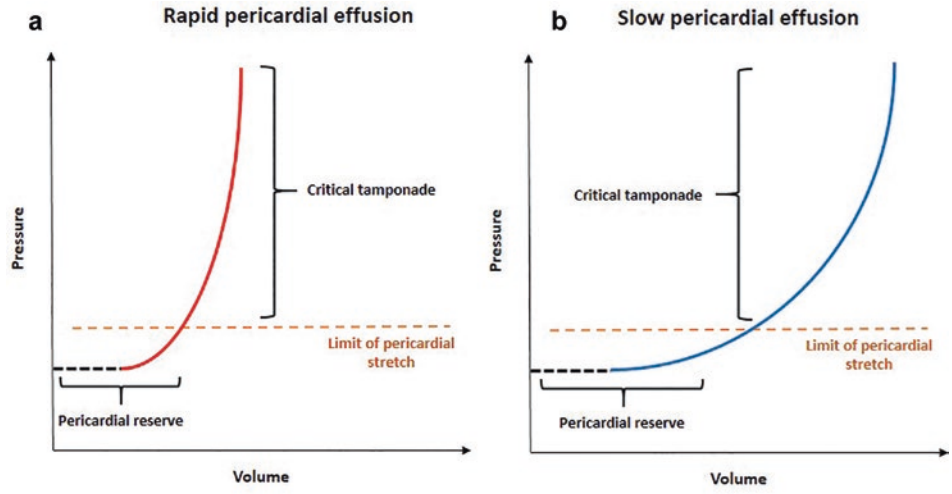

Fig. 46.1 Pressure/volume curves of the pericardium: (**a**) A rapidly building pericardial effusion is responsible for rapid hemodynamic deterioration. (**b**) A slower building pericardial effusion may reach a larger volume before it becomes clinically evident [1]

The interest of this case relies in the different elements that led to a delayed diagnosis of a progressive onset of cardiac tamponade during the hospitalization, as well as in the choice of the therapeutic strategy to be adopted to decompress the ventricles in this patient with a full stomach at the time of diagnosis.

Case Presentation

We present here the case of a 28-year-old man, with only a previous history of post-traumatic splenectomy 5 years earlier, no allergies, and no medication. He was admitted to the ICU following a severe chest trauma due to a crushing accident. At the scene, the patient had a hemodynamic failure with tachycardia at 130 beats per minute and arterial hypotension at 85/55 mmHg, as well as an acute respiratory failure with SpO_2 at 80% under 15 L/min oxygen therapy. He was intubated on scene, received 1 g of tranexamic acid, and had a vascular filling with 1 L of crystalloid. Then, he was transferred to the ICU.

The initial CT scan showed a bilateral hemopneumothorax without active bleeding, a pneumopericardium, extensive pulmonary parenchymal contusions, a bilateral rib flap, and a hemoperitoneum slide in the splenic compartment.

The blood test at the time of ICU admission was as follows: Hb, 11.8 g/dL; platelet, 187,000/µL; TP, 67%; and fibrinogen, 1.66 g/L. Troponinemia was elevated to 201 ng/mL, resulting in the diagnosis of myocardial contusion.

The blood gas analysis showed the following: pH, 7.24; PaO_2, 46 mmHg; $PaCO_2$, 40 mmHg; HCO_3^-, 17.6 mmol/L; lactate, 6.30 mmol/L.

Because of the hemodynamic instability, he was transferred to the operating room for an exploratory thoracotomy by bilateral clamshell incision: A large left pleural clot of 1.5 L was drained, and the exploration of the mediastinum revealed active bleeding from a diaphragmatic artery, which was ligated. It also showed a rupture of the posterior pericardium, which was sutured. The patient was transfused with 12 packed red blood cells, 8 fresh-frozen plasmas, and 1 platelet concentrate, and noradrenaline was required up to 3 mg/h to ensure satisfactory blood pressure.

At 24 h of management, the SOFA score was 10, and the ISS score was 29.

The day after the intervention, the patient was hemodynamically stable: He was normofrequent, was normotensive, weaned from catecholamines, and had no hyperlactatemia. Sedation was stopped, and he was extubated using high-flow oxygen therapy and noninvasive ventilation afterward. His neurological examination was normal, and he complained about chest pain related to the rib fractures leading to the placement of bilateral paravertebral catheters in T7–T8. Routine transthoracic echocardiography revealed a circumferential pericardial effusion less than 1 cm, without clinical manifestation.

Eight days after ICU admission, the events were marked by the progressive appearance of sinus tachycardia in the context of fever higher than 38.5 °C, associated with a biological inflammatory syndrome, and a purulent discharge from the paravertebral catheter. The diagnosis of paravertebral catheter infection was retained, and blood cultures were taken before the catheters were removed. Empirical antibiotic therapy with piperacillin-tazobactam was instituted. The inflammatory syndrome and the fever rapidly regressed, although the sinus

tachycardia persisted at 120 beats per minute. Transthoracic echography was not repeated in this context. At the same time, a left iliac thrombosis was detected on a follow-up scan and led to the initiation of curative anticoagulation.

Two days after the recovery, i.e., 10 days after admission, the patient's condition deteriorated: tachycardia worsened to 150 beats per minute, noninvasive blood pressure was 90/60 mmHg, and he complained of rest dyspnea with orthopnea. SpO_2 remained stable at 96% on room air, and auscultation remained unspecific apart from some bilateral ronchi. The patient was apyretic, conscious and oriented, and still in pain. His calves were supple, and there was no jugular turgor.

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46.2 Interventions

A transthoracic echocardiography was immediately performed, 96 h after the last control of the pericardial effusion. The examination revealed a significant increase in pericardial effusion quantified at 1 L, a paradoxical septum with notching of the right ventricle, protodiastolic collapse of the right ventricle, and a swinging heart (Fig. 46.2). The diagnosis of cardiac tamponade by probable hemopericardium

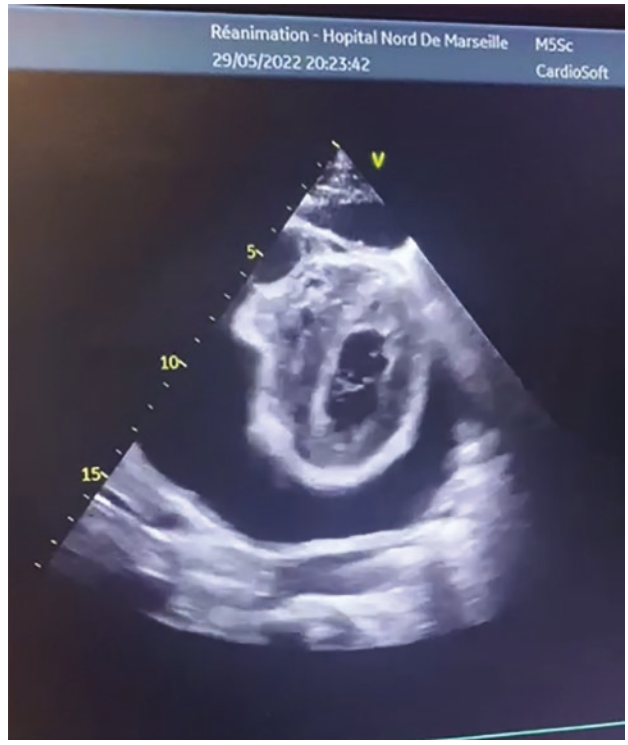

Fig. 46.2 Short axis ultrasound section: large circumferential pericardial effusion, paradoxical septum, right ventricular notch, and protodiastolic exclusion of the right ventricle

promoted by the introduction of curative anticoagulation was retained, and the thoracic surgeon was contacted urgently.

In the meantime, an arterial catheter was placed, and a paradoxical pulse was observed in this spontaneously ventilated patient.

46.3 Differential Diagnosis

It is extremely likely that the tachycardia presented by the patient in a febrile setting on day 8 was in fact the first clinical sign of cardiac tamponade. Nevertheless, it is an unspecific sign that had many other explanations in this patient.

Indeed, this tachycardia was initially attributed to paravertebral catheter infection, and this information was transmitted to the different reliefs in an automatic way, generating a collective fixation bias.

In addition, this patient had other reasons for being tachycardic: He was in pain, because of bilateral rib fractures whose surgical fixation was postponed due to infection. He was also anxious and sometimes agitated because of poor sleep quality and persistent dependence on noninvasive ventilation sessions.

Finally, the cardiac tamponade was responsible for an obstructive shock state with common differential diagnoses in the ICU: severe pulmonary embolism (which could have been the case in this patient with an iliac thrombosis) and compressive pneumothorax (on admission, the patient had a poorly tolerated bilateral pneumothorax).

In this uncertain clinical context, transthoracic ultrasonography remains the examination of choice to establish a diagnosis.

46.4 Treatment

The diagnosis of cardiac tamponade with hemodynamic repercussions was made at 9 pm, 2 h after the patient's last meal. In the context of probable hemopericardium, a surgical evacuation was decided after multidisciplinary discussion, in accordance with the European recommendations [2].

However, the question of the timing of the procedure in this non-fasted patient was a concern, and the surgical and anesthetic views were contradictory. As the patient did not require vasopressors, the surgeon considered him sufficiently stable to wait an additional 4 h to manage a fasted patient. On the other hand, our team, although fearing a poor tolerance of general anesthesia with positive ventilation, considered that the patient was likely to worsen, requiring an urgent decompression.

Finally, the time for discussion and mobilization of the different teams on call brought the patient to the operating room 6 h after his last meal. He was sedated with sevoflurane in a sitting position, maintaining spontaneous ventilation without fearing the aspiration risk. With additional local anesthesia, a 1 L hemopericardium was evacuated through a Marfan line, and a pericardial drain was left in place. The patient had no cardiac decompression syndrome, was not intubated during the procedure, and was transferred to the ICU postoperatively.

46.5 Evolution, Outcome, and Follow-Up

The postoperative evolution was favorable: At the return to ICU, the patient was no longer tachycardic, and his blood pressure was stabilized without catecholamines at 130/80 mmHg. The paradoxical pulse disappeared, as well as the dyspnea.

The ultrasonography control was satisfactory with normal cardiac contractility and regression of the pericardial effusion. The pericardial drain was removed on day 3 postoperatively.

The patient then improved in all aspects, and surgical fixation of the costal flaps was performed on the 20th day of admission. The infectious syndrome regressed, allowing antibiotic therapy to be stopped after 7 days of effective treatment, the various drains were removed, the pain was controlled by oral analgesics, and the patient was discharged to the surgical ward 1 month after his admission to the intensive care unit.

46.6 Discussion

The clinical case we have described is that of a delayed cardiac tamponade, following a post-traumatic hemopericardium. The formation of this pericardial effusion was slowly progressive and caused clinical signs that were unspecific for a long time, such as tachycardia, leading to manifest a delay in diagnosis. This delay was important as this is a rare pathology: Only a few cases of traumatic tamponade delayed in relation to the initial trauma are described in the literature [3]. The first lesson of this case is that any tachycardia occurring in a patient with a myocardial contusion must be investigated by transthoracic echocardiography, even when another cause can explain this tachycardia.

A second lesson is that the intensivist must remain cautious regarding the fixation bias, which can lead her or him to maintain a fixed point of view and to lose her or his global view of the case (in our case, to attribute tachycardia to fever without thinking again of the myocardial contusion) [4]. This fixation bias can also be transmitted during the shift: The information on tachycardia was transmitted as the consequence of an infection, generating a collective fixation bias from which no physician was able to emerge before the severe deterioration.

The treatment of tamponade is based on the evacuation of the pericardial effusion, which can be done either by needle pericardiocentesis when the effusion is clearly liquid, circumferential, and not septate or by surgical approach according to different routes [2]. In our center and in accordance with other studies [5], the anesthetic protocol in case of surgical evacuation of the effusion consists of sedation with the maintenance of spontaneous ventilation.

Cardiac tamponade is not a contraindication to intubation with positive pressure ventilation: In the case of a full stomach, it is recommended to proceed to a general anesthesia with rapid sequence intubation, after surgical drape with surgeons ready

to incise, and to ventilate with small tidal volume without any PEEP. Here, the contribution of gastric ultrasound was omitted in this urgent context: The literature is nevertheless favorable to its performance when doubt is present about the vacuity of the stomach of an urgent surgical patient. The anesthetic team could have used this tool to confirm or deny gastric emptiness 6 h after the last meal, in this urgent patient whose gastric emptying was most probably disturbed [6].

Take-Home Messages

- Any tachycardia in a chest trauma patient with myocardial contusion should be followed by a cardiac echocardiography, even at a distance from the trauma.
- Cardiac tamponade is not a contraindication to positive pressure ventilation, but anesthetic induction must be performed according to a well-established protocol.
- Point-of-care gastric ultrasound can effectively guide an airway management strategy in the ICU and the OR.
- The fixation bias is a major cognitive bias in healthcare and can lead to diagnostic delays.

Summary

Cardiac tamponade is a diastolic ventricular insufficiency responsible for a reduction in cardiac output. Most often the consequence of cardiac surgery or neoplasia, it can follow a thoracic myocardial contusion, even several days after the trauma.

The case presented here is that of a 28-year-old man who suffered a thoracic crush injury following a traffic accident, responsible for a bilateral hemopneumothorax, a bilateral flail chest, and a myocardial contusion. The patient presented 10 days after the trauma with hemodynamic deterioration related to a delayed cardiac tamponade on a 1 L hemopericardium.

The interest of this case lies in the presentation of this rare and urgent pathology, in the differential diagnoses and cognitive biases which led to a diagnostic delay, as well as in the description of the various therapeutic and anesthetic strategies to be known to effectively manage these patients.

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Polytrauma Patient with Refractory Shock

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Learning Objectives

- Learning objective 1: Approach to polytraumatized patient
- Learning objective 2: Pelvic fracture management
- Learning objective 3: ICU role in stabilization of polytraumatized patients

47.1 Introduction

Pelvic fractures are present in up to 25% of multiple-trauma patients [1]. They are usually associated with other injuries, and their management can be challenging for the physician. Despite all the improvements in trauma care, mortality remains high due to hemodynamic instability secondary to bleeding.

Implementation of a standardized initial approach to trauma patients avoids delays in the identification of life-threatening injuries, which could potentially increase the chances of the patient to survive. Thus, we use the Advanced Trauma Life Support (ATLS) recommendations, which provide a rapid sequence of action and are commonly used worldwide, with a primary assessment (A, airway; B, breathing; C, circulation; D, disability; and E, exposure), and a secondary assessment to comprehensively review all head-to-toe injuries. These recommendations define hemodynamic instability as the identification of a systolic blood pressure of <90 mmHg and/or a heart rate of >120 bpm and urge the clinician to look for bleeding in any patient fulfilling these criteria. Bleeding may be found "on the floor (from a visible wound) and four more": thoracic, abdominal, pelvic, and long bones.

The Intensive Care physician and the Intensive Care Unit (ICU) play a central role in the stabilization of the patient and in the triage of the injuries, together with multidisciplinary teams. This will allow to reduce the risks for the patient and will help identify the priority injuries to be addressed, including damage-control strategies, hemorrhage control, and definitive treatments.

Case Presentation

We present a 52-year-old female patient who was transferred to the hospital by the Emergency Medical Services (EMS), after falling from the fourth floor. Upon arrival of the EMS at the place where the incident took place, the physical examination of the patient revealed the following: (a) patent airway with bleeding; (b) spontaneous breathing, eupneic, SpO_2 87%; (c) sinus tachycardia (120 bpm) and mild hypotension (105/59 mmHg); (d) low level of consciousness, with a Glasgow Com Scale (GCS) of 3 points, otorrhagia, epistaxis, left palpebral hematoma; and (e) crepitus in both scapulae, suspected unstable pelvis, suspected fractures in the upper and lower limbs. The EMS stabilized the spine with a spinal board and cervical collar, proceeded to intubation and initiation of mechanical ventilation because of the low level of consciousness, placed an intraosseous access on the distal end of the right tibia and started crystalloid infusion, and placed a pelvic binder to stabilize the pelvis. Due to the suspected severity of the injuries, the patient was transferred directly to the ICU, without going through the Emergency Department. Upon arrival to the ICU, the patient was reassessed, the massive transfusion protocol was activated, and an early

body computed tomography (CT) was performed for detailed assessment.

The past medical history was notable by a drug-resistant partial temporal lobe epilepsy that had required left lobectomy. The patient was under chronic treatment with anticonvulsants, benzodiazepines, and neuroleptics.

47.2 Investigations

Physical examination on admission:
- Neurological: GCS 3, unreactive left mydriasis, and left periorbital hematoma, which limited palpebral opening.
- Respiratory: Intubated and connected to mechanical ventilation. Auscultation: adequate aeration of both hemithorax. Crepitus in both scapulae.
- Cardiovascular: Severe hypotension (60/38 mmHg), sinus tachycardia at 130 bpm, markedly prolonged capillary refill time.
- Abdominal: Distended, but soft, with no signs of peritoneal irritation. FAST: negative for free abdominal fluid and cardiac tamponade; full bladder.
- Limbs: Asymmetry of the lower limbs with shortening and rotation of the left side. First toes of the left foot bruised. Intraosseous line on the distal end of the right tibia.

Laboratory investigations on ICU admission:
- Complete blood count: Leukocytes, 14,900/mcL (70%N); hemoglobin, 9.8 g/dL; platelets, 166,000/mcL.
- Coagulation: Blood does not clot.
- Biochemistry: Sodium, 128 mmol/L; potassium, 4.7 mmol/L; chloride, 102 mmol/L; glucose 139 mg/dL; urea, 17 mg/dL; creatinine, 0.45 mg/dL; GOT, 281 U/L; GPT, 222 U/L; GGT, 55 U/L; bilirubin, 0.1 mg/dL; calcium, 7.28 mg/dL; phosphate, 2.59 mg/dL; magnesium, 1.2 mg/dL; CK, 545 U/L; procalcitonin, 0.04 ng/mL.
- Venous blood gas (VBG): pH, 7.25; pCO_2, 34 mmHg; bicarbonate, 15 mmol/L; lactate, 10 mmol/L.
- Arterial blood gas (ABG) after 1 h of hemostatic resuscitation: pH, 7.22; pCO_2, 44 mmHg; pO_2, 165 mmHg; bicarbonate, 18 mmol/L; ionized calcium, 3.9 mg/dL; lactate, 4.7 mmol/L.

Imaging investigations (Fig. 47.1):
- Brain CT scan:
  - Left frontal subdural hematoma
  - Subarachnoid hemorrhage with intraventricular hemorrhage
  - Multiple facial fractures
- Chest CT scan:
  - Aortic laceration
  - Large right pneumothorax and small left apical-anterior pneumothorax
  - Pulmonary contusion and bilateral atelectasis
  - Fractures of the 1st, 3rd, 5th, 6th, 7th, 8th, and 12th left ribs

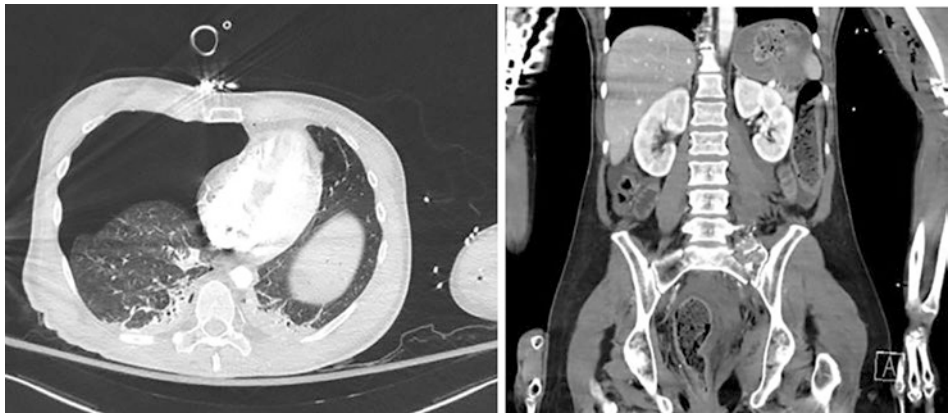

Fig. 47.1 Body CT scan (pneumothorax and pelvic fracture)

- Abdominal CT scan:
  - Comminuted fracture of the left sacral ala, oblique fracture of the right superior pubic ramus, and comminuted fractures of both iliopubic and ischiopubic ramus
  - Left iliopsoas and adductor hematoma
  - Hemoperitoneum secondary to active bleeding from the left internal iliac vein
  - Left femoral fracture, at the level of the neck

47.3 Differential Diagnosis

In a multiple-trauma patient presenting with shock, a differential diagnosis should be established rapidly (Fig. 47.2). Hypovolemic (hemorrhagic) shock is the most frequent cause of shock, being the first cause of death in this population. However, important causes of obstructive shock must be ruled out beforehand. In this case, the patient exhibited a combination of both mechanisms of shock; she had an obstructive shock secondary to tension pneumothorax and a hypovolemic shock due to active bleeding.

In addition, a differential diagnosis between stable and unstable pelvis must be carried out. Pelvic mechanical stability depends on the integrity of the bone complex and the set of ligaments that neutralize the stress forces, that is, the posterior complex of the pelvic ring (Fig. 47.3). Our patient has a mechanically stable pelvis, despite the hemodynamic instability, and presents with comminuted fracture of the left sacral ala, oblique fracture of the right sacral branch, and comminuted fractures of both iliopubic branches and ischiopubic ramus.

Hypovolemic	Obstructive	Distributive	Cardiogenic
Hemorrhage	Cardiac tamponade Tension pneumothorax Pulmonary thromboembolism	Neurogenic Metabolic acidosis Hypocalcemia Sepsis	Acute myocardial infarction Stress cardiomyopathy

Fig. 47.2 Differential diagnosis of shock

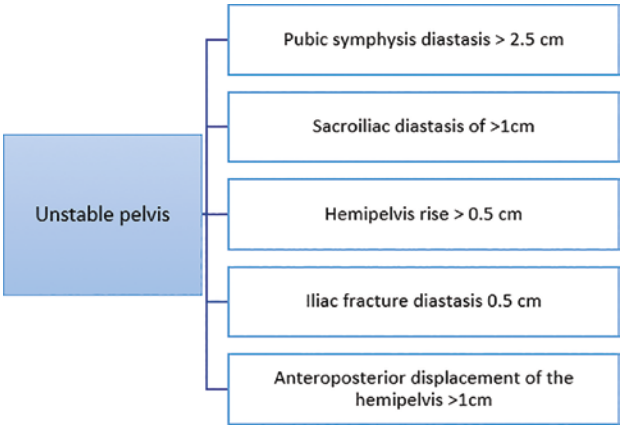

Fig. 47.3 Diagnostic criteria for unstable pelvis

47.4 Treatment

Upon admission, resuscitation with crystalloids was started, as well as blood products, with a transfusion of eight packed red blood cells, 2 units of fresh frozen plasma, 1 pool of platelets, 1 g of tranexamic acid, and 2 g of calcium. A hypertonic saline bolus was given for suspected increased intracranial pressure shown by anisocoria. Considering the CT findings, a right pleural drain was placed. In the following hours, intense resuscitation measures were continued, presenting refractory shock that required massive transfusion to achieve a hemoglobin concentration of >7 g/dL and high-dose norepinephrine (up to 1.20 mcg/kg/min).

47.5 Evolution, Outcome, and Follow-Up

A multidisciplinary team was involved in the care of the patient, with an assessment of the potential alternatives for the definitive management of hemorrhagic shock of the patient:

- Interventional Radiology: Embolization of an active bleeding from the left internal iliac vein was not technically feasible, as per the venous origin of the bleeding.
- Vascular Surgery: The aortic injury would be amenable to endovascular treatment, once the patient would be stable. However, there were no surgical alternatives to control the venous bleeding.
- Orthopedic Surgery: The possibility of stabilizing fractures was considered, which was rejected by the anesthesiology team, since any surgery would be contraindicated that was not aimed at controlling bleeding.
- General Surgery: Pelvic packing was considered, but it was rejected because the risk of death during the procedure was considered greater than the possible benefit.
- Neurosurgery: Ventricular drain was placed.

Despite resuscitation, the patient progressively worsened toward a situation of refractory shock, with lactate levels rising to 14 mmol/L. After 48 h of treatment, a decision to withdraw life support was made together with the medical team and the relatives. Norepinephrine was stopped, and terminal extubation was performed. The patient died.

47.6 Discussion

In the case we present, the main life-threatening injury was pelvic trauma. The patient presented other serious injuries with high morbidity and mortality, such as aortic laceration. However, this was a contained vascular injury, which did not cause active bleeding and, therefore, was not the cause of the patient's hemodynamic instability. Despite advances in the care of trauma patients, mortality from severe pelvic fractures remains high (up to 60%), much of it attributable to uncontrolled bleeding [2]. One way to classify pelvic injury is the WSES classification (World Journal of Emergency Surgery), which includes the type of injury (Young and Burgees), the mechanism of action, and the hemodynamic status of the patient [3].

There are three pillars of hemorrhagic focus control: hemostatic resuscitation with activation of massive transfusion protocols, mechanical stabilization, and preperitoneal pelvic tamponade (packing) and/or embolization. Mechanical stabilization can be achieved quickly, using a pelvic girdle or sheet; fixation can subsequently be carried out with an external fixator or a C-clamp. Packing is a measure that reduces mortality, useful for venous bleeding (80% of cases). If bleeding persists after packing, arterial bleeding should be suspected, and, thus, arteriography should be pursued for diagnosis and therapeutic embolization. An alternative in unstable patients is the placement of an intra-aortic balloon via the femoral artery, to temporarily control bleeding and preserve blood flow in vital organs. However, this is an invasive technique with potential complications and is still associated with high mor-

tality rates. In our case, the patient presented a profound hemodynamic instability, which discouraged the performance of damage control measures such as packing.

Take-Home Messages

- Hemorrhage is the leading cause of mortality in multiple-trauma patients. A trauma patient presenting with shock should prompt the possibility of bleeding, once obstructive shock has been ruled out (tension pneumothorax, cardiac tamponade, etc.).
- Pelvic trauma is associated with a high mortality (up to 60%) despite advances in the care of multiple-trauma patients, essentially due to uncontrolled bleeding.
- The management of a patient with pelvic trauma and hemodynamic instability is based on three pillars: resuscitation, mechanical stabilization, and damage control through packing/embolization.

Summary

We present a multiple-trauma patient, where the main injury mechanism was a fall, with vertical impact. In the initial evaluation according to the ATLS, she presented a patent airway, spontaneous breathing with an oxygen saturation of 87%, hypotension and tachycardia, Glasgow Coma Scale (GCS) score of 3 points, and several fractures in her limbs. After initial hemodynamic stabilization (crystalloids and blood transfusion), body CT was performed, which revealed multiple facial fractures, tension pneumothorax, aortic laceration, and multiple pelvic fractures, with an active venous bleeding. The patient evolved to a refractory shock state, and both interventional and surgical approaches were discarded due to the complexity of the lesions. The patient died after withdrawal of life support.

Acknowledgments We would like to acknowledge all the ICU staff, as well as the Emergency Medical Services, and the Departments of General Surgery, Orthopedic Surgery, Vascular Surgery, Neurosurgery, and Interventional Radiology at Hospital Universitario Río Hortega, Valladolid, Spain.

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Resuscitative Endovascular Balloon Occlusion of the Aorta (REBOA) in a Patient with Exsanguinating Penetrating Torso Trauma: A Clinical Case

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Contents

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Learning Objectives

- The importance of ABCDE assessment
- The importance of having structured protocols in the initial care of a trauma patient
- Management of unstable penetrating torso trauma
- Principles of damage control resuscitation
- When to implement the use of a REBOA: indications and process

48.1 Introduction

Haemorrhagic shock remains a leading cause of potentially preventable death among injured patients, and non-compressive abdominopelvic haemorrhage is one of the pathologies with higher morbidity and mortality rates in this group [1]. This has led to the development of new devices to control bleeding, including the resuscitative endovascular balloon occlusion of the aorta (REBOA). Non-compressible abdominopelvic haemorrhage is defined as massive abdominal and/or pelvic bleeding that cannot be controlled by direct compression, and mortality can be as high as 45%. Multiple studies have suggested REBOA to be a safe and effective alternative to emergency thoracotomy in these patients and has gained popularity as a minimally invasive alternative [2]. Endovascular or open aortic occlusion in abdominal or pelvic haemorrhage aims to redistribute the circulating volume and prevent cardiocirculatory arrest, increasing the opportunity for definitive control of bleeding through surgery or angioembolization. Occlusion of aortic flow using REBOA results in a change in volume distribution and an increase in blood pressure, improving coronary and cerebral perfusion [3]. This paper describes one case in which REBOA was used in a patient with penetrating abdominal trauma and haemorrhagic shock associated.

Case Study

A 22-year-old male patient, with no medical background, was admitted to the emergency department (ED) at 5:00 am due to penetrating torso trauma.

First contact with the prehospital emergency services occurred at 4:23 am, unknown time of trauma. Upon arrival of the emergency services to the scene, the patient presented a systolic blood pressure (SBP) of 60 mmHg and heart rate (HR) of 65 bpm, with a clear chest upon auscultation and a normal respiratory rate with 95% O_2 saturation (O_2sat) at ambient air. He had a Glasgow Coma Scale (GCS) score of 9/15 (eye-opening of 3, best motor response of 5, and verbal response of 1). He presented a penetrating wound in the right thoraco-abdominal region, under the xiphoid process, with active bleeding that disappeared when compressed. No weapon was found. FAST was performed, which was positive for free fluid in the abdomen and pelvis and negative in the thorax (no pericardial effusion). Rapid sequence intubation was performed, and fluid resuscitation was started for an SBP objective of 90 mmHg (total administered upon hospital admission: 300 mL of saline 0.9%). He was then transferred to our centre, maintaining

haemodynamic stability and 100% O_2sat after orotracheal intubation.

After notification of the patient's injuries and status by the emergency services, the leader of the Trauma and Emergency ICU team in our hospital activated our protocol for massive haemorrhage and alerted cardiac and general surgeon's teams. The correct equipment in the box of our trauma bay was checked.

Upon arrival at the trauma bay (5:00 am), the handover of the patient took place, at that moment central pulses and airway patency (isolated) were noted, the team leader received the rest of the information gathered by the prehospital emergency services and the patient was monitored with O_2 sat, end-tidal CO_2 ($etCO_2$), continuous ECG and non-invasive blood pressure (BP). Then, the primary survey was performed, and only when the patient was stabilized and the adjunct tests had been performed, a partial secondary survey was performed. Routine laboratory tests, thromboelastometry (ROTEM), arterial gas blood test, ethanolaemia, and urine sample (testing for drugs of abuse) were performed. Blood was sent for typing and cross-matching.

Primary survey:

X: No external bleeding was detected. ABCD resequencing was not needed.

A (Airway): patent airway isolated with orotracheal tube n° 8 and connected to invasive mechanical ventilation (IMV). Reliable waveform capnography with $etCO_2$ of 33 mmHg.

B (Breathing): His chest rising was symmetrical without any laceration or abrasion. Chest auscultation was clear, and there was no tenderness. No tracheal shift was found. He had an O_2sat of 100% with IMV: Volume-control FiO_2 of 100%, PEEP of 5 cmH_2O, tidal volume of 500 mL and respiratory rate of 18 bpm.

C (Circulation): Haemodynamically unstable; BP, 90/53 mmHg; HR, 70 bpm. Central pulses were present and symmetric, with capillary refill of 3 seconds, and right radial pulse present. Venous accesses: two large-bore peripheral catheters.

D (Disability): RASS -5 under sedoanalgesia effects; pupils: normal size and reactive.

***E (Exposure*)**: Temperature (peripheral): 36 °C. He had an incised wound of about 3 cm at the level of the sternal border (right parasternal), with exposure of muscular tissue, and bleeding contained by direct compression with gauzes.

Extended FAST was performed, which was positive for free fluid in the abdomen and pelvis, negative in the thorax with no pericardial effusion (◘ Fig. 48.1). Systolic BP started to decline in the next measurements (80–85 mmHg), and intravenous norepinephrine infusion was started peripherally as we placed a femoral central venous introducer sheath. Transfusion with packed red blood cells (RBC) was started using an infuser, and we placed a femoral arterial line with a 5 Fr introducer sheath. The arterial gas blood test showed metabolic acidosis with pH of 7.20, HCO_3^- of 15.6 mmol/L, BE of −11.8, lactate of 4.2 mmol/L and Hb of 11.1 g/dL. After 4 units of packed RBC transfusion, haemodynamic stability was achieved with systolic BP of 110 mmHg and HR 80 bpm, with a 0.2 mcg/kg/min infusion rate of norepinephrine. We performed chest and pelvic X-rays, which showed no alterations or lines of fracture.

While awaiting the general surgery team response, a rapid secondary survey was conducted. The patient had erosions and a haematoma in the right superciliary region and a left retroauricular cephalohaematoma. He also presented crepitation

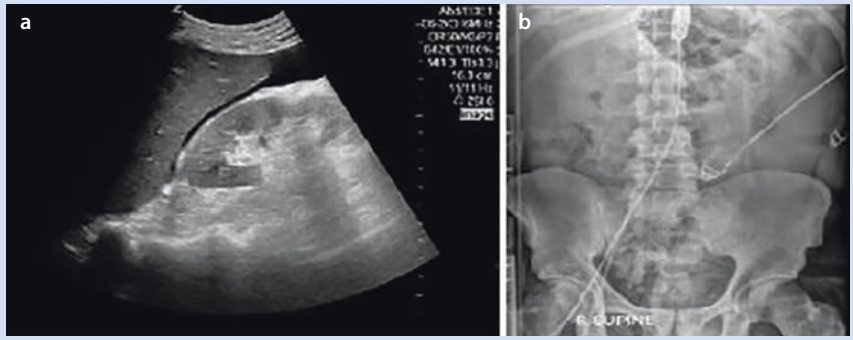

Fig. 48.1 (**a**) Positive FAST for free abdominal fluid on arrival to ED. (**b**) X-ray after zone I REBOA implantation

on palpation with subcutaneous emphysema on the right parasternal wound that extended to the right anterior pectoral region. No other injuries were found. The back of the patient couldn't be examined.

At that time (5:30 am, +30 min from admission), the patient started with new-onset hypotension with BP down to 60/54 mmHg and tachycardia of 110 bpm (Fig. 48.2). The rate of infusion of blood products and norepinephrine was increased until 250 mL/min and 0.6 mcg/kg/min, respectively, but with minimum recovery of blood pressure, to a maximum of 85 mmHg SBP, showing progressive abdominal distention.

On suspicion of an abdominal origin of the haemorrhagic shock, and as a bridge to arrival at the operating room (OR), we decided to place a REBOA in zone I (REBOA Medical AS, Bastad, Norway; Reboa Medical brand, an 8 mL balloon, and a 6-Fr introducer sheath), following our unit's protocol [4]. We used the previous femoral arterial line as a guide, and after placement, the balloon was filled slowly with a 6 mL contrast solution, with increased non-invasive arterial pressure in the left arm to 140 mmHg systolic BP. The initial X-ray control showed infra-diaphragmatic placement of the balloon, remaining in zone II. It was deinflated and progressed to zone I, and correct positioning was verified with new radiological control (Fig. 48.1). After that, an immediate increase in systolic BP was obtained (up to 170 mmHg), which allowed to stop norepinephrine and blood product infusion. Time of balloon inflation: 5:40 am (+40 min from admission).

While placing the REBOA, the general surgery team arrived and prepared the OR, and he was immediately transferred there. Upon arrival, he had received a total transfusion of 17 units of packed RBC, 4 units of fresh frozen plasma, and 2 platelet pools. REBOA inflation time exiting the ICU to the OR was 17 min. At the OR, handover took place and emergency laparotomy was performed. Once initial packing and control of active bleeding of the gastroduodenal artery was achieved, the balloon was deinflated slowly (over 3 min), ensuring that no new bleeding or haemodynamic destabilization occurred. Total occlusion time: 45 min.

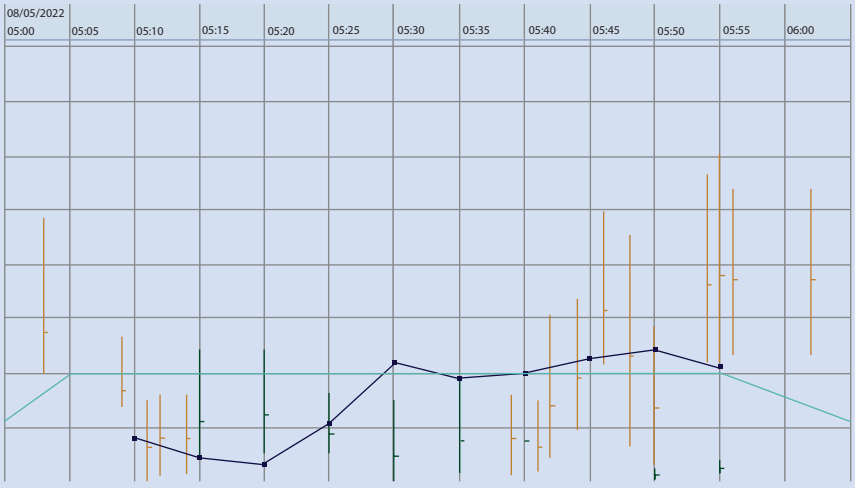

Fig. 48.2 Non-invasive blood pressure (NIBP, orange lines). Invasive arterial pressure (IAP, green lines). Heart rate (HR, dark blue line). O_2 saturation (O_2sat, light blue line). Superior line: date of admission and timeline. Upon admission NIBP and O_2sat were monitored. Patient presented with hypotension (90/53 mmHg), but HR was 75 bpm. Vasoactive drugs and transfusion of blood products were started with a rapid infuser through a large-bore sheath introducer. Arterial femoral line access was gained, and IAP was monitored (green lines). Patient deteriorates haemodynamically with hypotension and tachycardia despite augmenting vasopressors and infusion rate, and a decision to place a REBOA was made (05:30), using the arterial line already placed as guide (monitoring again NIBP, orange lines). When inflation of REBOA occurs, there is a shift of systolic arterial blood pressure from 85 mmHg to 140 mmHg. Afterward, correct positioning was checked

48.2 Investigations

Laboratory tests:

- **Arterial gas blood test**: pH, 7.20; pCO_2, 40 mmHg; pO_2, 585 mmHg; HCO_3^-, 15.6 mmol/L; BE, −11.8 mmol/L; K+ 3.2, mEq/L; glucose, 160 mg/dL; haemoglobin, 11.1 g/dL; Na^+, 137 mEq/L; Cl^-, 112 mEq/L; Ca^{++}, 1.01 mmol/L; lactate, 4.2 mmol/L.
- **Blood test general analysis**: RBC, 3.70 xmill/μL; haemoglobin, 11.4 g/dL; platelets, 59 × 1000/μL; leukocytes, 7.2 × 1000/μL (N 74.6%, L 17.7%, M 7.4%, E 0.1%, B 0.2%); creatinine, 0.73 mg/dL; glomerular filtration rate (ckd-epi), 61 mL/min/1.73 m^2; ALT (GPT), 207 U/L; AST (GOT), 415 U/L; GGT, 33 U/L; FA, 43 U/L; LDH, 398 U/L; bilirubin, 3.8 mg/dL; CK, 410 U/L; urea, 21 mg/dL; prothrombin activity, 58%; INR, 1.53; TTPa, 35 s; fibrinogen, 87 mg/dL.
- Ethanol and drugs of abuse were negative.

Imaging tests:

- Chest X-ray: No signs of pneumothorax or pneumomediastinum. No signs of free pleural fluid or occupation, no infiltrates. No signs of fractures
- Pelvic X-ray: No signs of fractures. No increased soft tissue

48.3 Differential Diagnosis

Post-traumatic bleeding shock was our primary suspicion diagnosis, but other causes of hypotension had to be considered:

- Obstructive shock can occur in the setting of tension pneumothorax and cardiac tamponade, which in this case was ruled out in the primary evaluation (no hypoventilation or jugular vein ingurgitation) and by performing an extended FAST with no pericardial effusion, as well as a chest X-ray with no signs of pulmonary or pericardial pathologies (Fig. 48.1).
- Cardiac contusion in the context of trauma can result in cardiogenic shock, which was also discarded in the initial FAST performed.
- Neurogenic shock may also be suspected in case of traumatic spinal cord involvement. This type of shock is suggested by an inappropriately low heart rate in the setting of hypotension, which was not the case with our patient, as his BP raised up to 110 bpm. The probable trajectory of the wound (anterior and at low thoracic level) made it also improbable.
- Finally, other causes should be considered that are not related to trauma or blood loss, such as septic shock and toxic causes, much less probable in this case.

Concerning bleeding shock, it is important to establish a differential diagnosis of the bleeding source to guide the therapy. In this case, due to the location of the external thoracoabdominal wound, with unknown extension or trajectory (weapon was not found), the main suspicious areas of internal bleeding were the thorax, abdomen, pelvis, or retroperitoneum:

- The absence of pleuro-pericardial effusion on FAST made intrathoracic bleeding unlikely, and due to the location of the wound with normal pelvic X-ray, abdominal origin was considered more plausible than pelvic bleeding.
- Note that retroperitoneal haemorrhage cannot be ruled out by FAST or X-rays.

48.4 Treatment

Upon arrival at the ED, treatment was started in parallel to the primary survey and adjunct tests, following the principles of damage control resuscitation. This included haemostatic resuscitation (avoiding aggressive fluid resuscitation) and activation of massive bleeding protocol, initiation of vasopressors and constant re-evaluation of hemodynamic status while advancing in diagnosis. The patient received a total of 17 units of packed RBC, 4 units of fresh frozen plasma and 2 platelet pools at our trauma bay. Upon haemodynamic deterioration despite all these measures, REBOA was implemented to control non-compressible torso haemorrhage. Since the abdomen was considered the probable source of bleeding, it was decided to perform a zone I REBOA.

At this point, we were facing a case of penetrating torso (most probably abdominal) injury with important hemodynamic instability, for which direct emergent exploratory laparotomy is recommended, with no time to perform other imaging tests. Once REBOA achieved temporary control of bleeding, the patient was transferred to the operating room. Intra-operative findings were massive haemoperitoneum and large retroperitoneal haematoma, hepatic laceration of segment 5,

gastroduodenal artery and bile duct laceration, and signs of pancreatitis. Arterial ligation, T-T reconstruction of the biliary duct and abdominal packing was performed, while he continued to receive transfusion in a balanced ratio.

Back at the ICU, he developed multiorgan failure and coagulopathy, in which reperfusion-injury by REBOA may have played a role, besides primary lesions and damage control surgery. The device and its introducer sheath were promptly removed after surgery.

48.5 Evolution, Outcome, and Follow-up

The patient had a slow recovery and was finally discharged from our Intensive Care Unit on day 28 of evolution, after presenting various complications during his stay:

- After initial surgery, he presented with abdominal compartment syndrome, with associated renal failure that required renal replacement therapy. Surgical revision was performed, and vacuum-assisted therapy was placed on day 12. Periodical surgical revisions were performed, and abdominal wall closure was feasible on day 23. He also developed biliary tract obstruction treated with internal-external biliary drainage, acute post-traumatic pancreatitis and bacteraemic secondary peritonitis by Proteus Mirabilis treated with meropenem and empirically with anidulafungin. Biliary drainage was retired on day 16.
- He developed post-traumatic portal and inferior mesenteric venous thrombosis for which he received anticoagulation with low-molecular-weight heparin. They had resolved in radiological control on day 13.
- Percutaneous tracheostomy was performed on day 16, and the patient was decannulated on day 27 after admission, prior to discharge from our ICU.

He was discharged from our hospital after 49 days with a good neurological status and oral nutritional tolerance.

48.6 Discussion

In this clinical case, we show successful placement of REBOA, allowing aortic control in penetrating abdominal trauma, optimizing cerebral and coronary flow until the patient could be transferred to the OR for definite control of the haemorrhagic source. It is an adjunct therapy for non-compressible torso injuries that still raises controversy concerning indication and its implementation in trauma centres [3, 5].

In this case, the information provided by the emergency services and the initial assessment on arrival at the ED, with a careful primary survey and the adjunct tests (especially FAST) were of utmost importance for the diagnosis and to guide management. The patient fulfilled the criteria according to our protocols to consider preactivation of the Massive Haemorrhage Protocol and be alert as to the need to implement a REBOA strategy.

Concerning haemostatic resuscitation, in this case, the patient did not receive our prespecified ratios of blood products, due to problems with the arrival of the complete packages (initially only packed RBC arrived). Coordination with other services

and constant revision of our practices are fundamental in the attention to the trauma patient.

Upon deterioration of haemodynamic status, REBOA was accomplished quickly and with immediate good results, increasing systolic blood pressure from 85 to 140 mmHg. Time from the decision to correct placement of REBOA is considered a critical step in cases of exsanguinating torso haemorrhage. In this case, the decision to use a femoral arterial line on arrival to the ED was made according to our protocol, since it facilitates quick cannulation if needed (as reported in other studies). Positioning is another important part of the process; in this case, it was verified with X-ray, and unadvertised placement in zone II was immediately corrected. Optimal occlusion time is not yet accurately defined, and 20 min is the most reported as safe in the literature (with a maximum of 60–90 min); in this case, occlusion time was 45 min, but performing a 'partial REBOA' inflation, and with no thromboembolic or reperfusion events [4].

We would like to underline the importance of elaborating protocols and providing training in this kind of less common and complex technique, so they can be successfully achieved in an emergency. Finally, teamwork within the trauma bay must be very coordinated, and it is what truly makes possible good outcomes in these emergent settings.

Take-Home Messages

- Penetrating torso trauma is a time-dependent pathology. Preactivation of the trauma team by the emergency services is of utmost importance for anticipating the situation we encounter and coordinating our response, if needed, with other specialists.
- Primary survey and adjunct tests are important to determine the origin of shock, initiating parallel saving measures while deciding optimal management.
- Limitation of fluid administration, control of temperature and coagulopathy, and balanced transfusions are key components of damage control resuscitation in penetrating trauma.
- Development and implementation of massive haemorrhage protocols is crucial. Revision should be made regularly since coordination with other services is complex but necessary.
- Emergent exploratory laparotomy is mandatory in unstable penetrating abdominal trauma.
- REBOA is an adjunct therapy for non-compressible torso haemorrhage. It provides a safe and effective alternative to emergency thoracotomy.
- Protocols and training are needed to help with decision-making (indication of the device), guide its placement, and optimize time to inflation.
- Placement of an arterial femoral line in selected patients that may end up benefiting from this therapy can shorten time to inflation.
- Optimal occlusion time is not yet accurately defined, aim should be 20 min, with a maximum of 60 min to avoid complications.
- Coordination in the emergent setting is key. Teamwork at the trauma bay made possible quick evaluation and treatment of this patient, including successful accomplishment of an unusual technique, and rapid transfer to the OR.

Summary

Haemorrhagic shock remains the leading cause of potentially preventable death among injured patients. Non-compressive torso haemorrhage is one of the pathologies with higher morbidity and mortality in this group, leading to the development of devices such as the resuscitative endovascular balloon occlusion of the aorta (REBOA).

This paper describes a case of a 22-year-old male patient who was admitted to the Emergency Department (ED) on May 8 due to penetrating torso trauma, in whom a REBOA was used. After notification of the patient status by the emergency services, the protocol of massive haemorrhage was activated, and cardiac and general surgeon's teams alerted. Upon arrival at the ED handover took place, a primary survey was conducted (no re-sequencing needed). FAST was performed upon haemodynamic instability and positive for free-fluid abdomen; norepinephrine and transfusion with blood products were started with an infuser; and femoral arterial line was placed, with initial stabilization that allowed performing other adjunct tests.

The patient status deteriorates (+30 min after admission) requiring increased infusion rates, and on suspicion of haemorrhagic shock of abdominal origin, we performed a zone I REBOA using previous arterial line as a guide (+40 min), with an increase of systolic blood pressure from 85 to 140 mmHg. He was transferred to the operating room (OR) for emergent exploratory laparotomy, controlling gastroduodenal artery bleeding and solid organ lacerations and lesion of the bile duct. The occlusion time of REBOA was 45 min.

The patient developed no lower limb thromboembolic or reperfusion events. He presented complications related to primary injury and related to surgery and care but was discharged from the ICU on day 28 and from the hospital on day 49, with good neurologic outcome and oral nutritional tolerance.

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Principles and Management of Haemorrhagic Shock

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Contents

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Learning Objectives

- Review the pathophysiology of haemorrhagic shock.
- Describe a diagnostic approach to the patient with suspected haemorrhagic shock.
- Review the key management considerations for haemorrhagic shock resuscitation.

49.1 Introduction

Haemorrhagic shock is a life-threatening manifestation of intravascular volume depletion due to acute blood loss. It belongs to the broader category of hypovolemic shock, one of the four classic groupings of shock (the others being distributive, obstructive and cardiogenic). Although often associated with either blunt or penetrating trauma, haemorrhagic shock may also commonly manifest in patients with gastrointestinal, urological, vascular, and obstetric pathologies. Such patients can present dramatically with external bleeding or with more subtle physiological signs suggestive of internal bleeding. In many cases, haemorrhage is a preventable cause of death, and early recognition and treatment are vital to ensure survival. This chapter will review the pathophysiology of haemorrhagic shock to better appreciate the urgency of definitive therapy, as well as key diagnostic and management considerations.

49.2 Pathophysiology

Major haemorrhage is variably defined in the literature either on the basis of transfusion requirement (e.g., requirement of ≥4 units of packed red blood cells within a 1 h period), estimated blood loss (e.g., postpartum haemorrhage with >1000 mL blood loss within 24 h of delivery), or physiological response (e.g., bleeding and a systolic blood pressure <90 mmHg or heart rate >110 beats per minute) [1].

Haemorrhagic shock results when oxygen delivery does not meet cellular oxygen demand. Significant blood loss leads to inadequate oxygen delivery to vital organs, activating numerous compensatory homeostatic mechanisms. The transition from aerobic metabolism to anaerobic metabolism leads to the accumulation of lactic acid, inorganic phosphates, and oxygen radicals. Progressive ATP depletion ultimately leads to cell death.

Systemic responses to haemorrhage include vasoconstriction of ischaemia-tolerant vascular beds such as the skin, muscle, and gastrointestinal tract to preserve flow to ischaemia-sensitive organs [2]. Increased central sympathetic tone and reduced parasympathetic outflow lead to tachycardia and increased cardiac contractility to maintain oxygen delivery. Hypoperfusion, pain, and local tissue injury may all trigger intense vasoconstriction to constrict blood flow and decrease bleeding. If haemorrhagic shock persists, however, compensatory vasoconstriction will eventually decompensate to a vasodilatory shock state. Circulating prostanoids, reactive oxygen species, and nitric oxide contribute to this vasodilation and exacerbate endogenous catecholamine hyporesponsiveness. In this late phase of decompensation, even blood transfusion may not restore normal intravascular pressures [3].

Tissue injury also leads to increased thrombin generation, platelet activation, and decreased fibrinolysis to help increase clot formation and stop bleeding. Coagulopathy

may occur when the coagulation system becomes overwhelmed and can be exacerbated by hypothermia and acidaemia (the 'lethal triad'). Plasma coagulation enzyme activity decreases by 10% with each 1 °C change in temperature and to <50% of normal when pH is <7.20 [1]. Aggressive crystalloid and colloid resuscitation can further dilute the circulating volume and worsen coagulopathy. Importantly, trauma-induced coagulopathy is a distinct entity associated with endothelial damage rather than dilutional resuscitation. Exposure to high levels of circulating catecholamines and cytokines disrupt endothelial cell function and the glycocalyx. Upregulation of protein C expression, dysregulation of von Willebrand factor, platelet dysfunction, and hypofibrinogenemia are all hallmarks of this process, which is associated with higher transfusion requirements, organ failure, and mortality [4].

49.3 Diagnostic Approach

Early recognition and prompt treatment of haemorrhagic shock are vital. Rapid control of haemorrhage and restoration of circulating volume reduce the severity, duration, and sequelae of the shock state. Delays in recognition and definitive treatment may lead to irreversible shock, multiorgan failure, and death.

The initial evaluation of the patient should focus on the history of presenting complaint and align this with potential sources of bleeding. There should be a low threshold to consider bleeding as the cause of shock in at-risk patients such as those with chronic liver disease, underlying coagulopathy, known vascular or gynaecological pathology, recent surgery, or trauma.

Patients with occult internal bleeding may present with subtle physiological signs and symptoms and diagnosis may be delayed, unlike patients with obvious active external bleeding. Those with normal physiological reserve may lose up to one-third of their circulating blood volume before hypotension is apparent. Tachycardia, narrow pulse pressure, tachypnoea, anxiety, and cool peripheries with pale skin or mottling may be earlier indicators of haemorrhage [5]. A Shock Index (SI) greater than 1.0 (calculated as the heart rate divided by systolic blood pressure) may be a better indicator of the severity of injuries, need for blood transfusion, and emergent operative management than hypotension alone [6]. The American College of Surgeons Committee on Trauma classify haemorrhagic shock by estimated blood loss (Table 49.1). Patients with more than 2 L of blood loss will generally have a significant tachycardia, hypotension, tachypnoea, and altered conscious state.

Anatomical sources of bleeding can be investigated rapidly by ultrasound or computed tomography. Focused assessment with sonography for trauma (FAST) is now a routine component of initial trauma patient evaluation. Ultrasound may be a valuable investigation for intrathoracic and intra-abdominal bleeding in the trauma setting [7], as well as for ruptured abdominal aortic aneurysm (AAA), ruptured ectopic pregnancy, and uterine bleeding in the non-trauma setting [8]. Computed tomography (CT) is a non-invasive imaging modality with high specificity but should not delay definitive interventions in unstable patients. Angiography is another important diagnostic and therapeutic tool for the actively bleeding patient [9].

Falling haemoglobin level, although important as a diagnostic marker of bleeding, is a late finding. A normal haemoglobin level does not exclude active bleeding

Table 49.1 The ATLS classification of haemorrhagic shock [5]

	Class I	Class II	Class III	Class IV
Blood loss in %	<15	15–30	30–40	>40
Pulse rate	<100	100–120	120–140	>140
Blood pressure	Normal	Normal	Decreased	Greatly decreased
Pulse pressure	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate	14–20	20–30	30–40	>35
Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Urine output (mL/h)	>30	20–30	5–15	Minimal

early in its course, and a focus on physiological signs and clinical evaluation should prompt action rather than the laboratory results when the history is suggestive of haemorrhage. Other laboratory markers of importance in haemorrhagic shock are lactate and base deficit, which can be quickly obtained from arterial blood gas analysis to monitor the severity of the shock state and resuscitation response. The coagulation profile, which should include platelet count, international normalised ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen, can indicate risk of further bleeding as well as severity of coagulopathy as a consequence of bleeding. Viscoelastic testing, such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM), may provide earlier information on coagulopathy in an active resuscitation scenario to guide transfusion strategy.

49.4 Management Considerations

A 'chain of survival' has been described [10] for haemorrhagic shock, commencing in the prehospital setting and continuing with resuscitation, definitive interventions, and post-haemostasis management in hospital (Fig. 49.1). Priorities in the prehospital setting are to minimise further exsanguinating blood loss, provide limited resuscitation, prevent hypothermia, and promptly transport the bleeding patient to a medical facility ('scoop and run') with capabilities to handle ongoing resuscitation and provide the necessary definitive care (e.g. a 'trauma centre' or hospital with surgical, obstetric, or endoscopy capabilities). Bleeding from compressible sites, such as limbs, should either be controlled with direct compression or proximal tourniquet if practicable prior to transfer.

Priorities in hospital are restoration of intravascular volume and definitive control of haemorrhage. Volume restoration should focus on the use of blood products, or whole blood, rather than isotonic fluids. Crystalloid resuscitation should be lim-

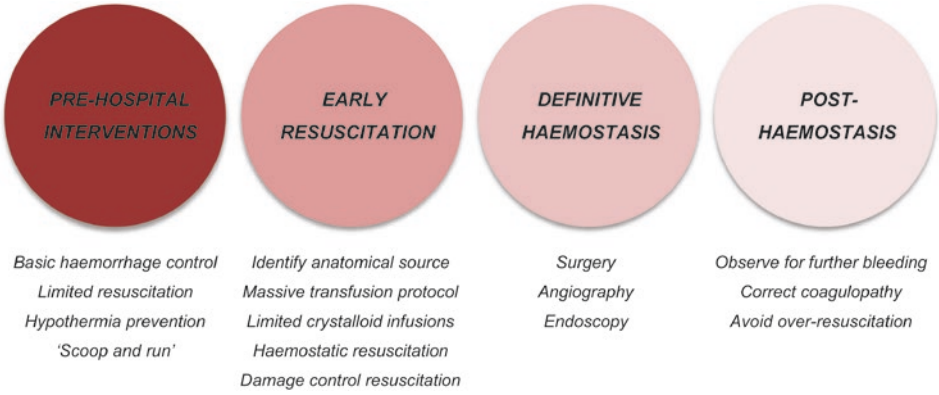

Fig. 49.1 The 'chain of survival' for haemorrhagic shock patients. Adapted from Cannon (2018), Hemorrhagic shock [10]

ited to less than 3 L in the first 6 h [11]. Hospitals should have established massive transfusion protocols to ensure timely delivery of blood products to the resuscitation room, as well as urgent access to uncrossmatched type-O blood in unstable situations. Delays in activating a massive transfusion protocol are associated with a 5% increased risk of mortality for every minute delay in initial blood product arrival [12].

49.4.1 Transfusion Strategies

There remains considerable interest in optimal transfusion strategies for bleeding critically ill patients. The European Society of Intensive Care Medicine's clinical practice guideline suggests the use of a high-ratio fresh frozen plasma (FFP) and red blood cell (RBC) transfusion strategy (i.e. either 1:1 or 1:2 FFP:RBC) for trauma patients [13]. The evidence is more sparse in non-trauma settings, but many hospital systems may utilise similar transfusion ratios for these patients based on extrapolated trauma data as well as to ensure uniformity in massive haemorrhage response. Currently, no strong recommendations can be made for the use of cryopreserved platelets, prothrombin complex concentrate, or empiric fibrinogen replacement.

Electrolyte monitoring is important for patients receiving massive transfusion. Hypocalcaemia is a common occurrence due to citrate accumulation from transfused products. Hyperkalaemia may also occur in the setting of ischaemic tissue washout, acidaemia, and lysis of transfused red blood cells [2]. Hypothermia should be anticipated early, and blood warming systems, passive (e.g. warmed resuscitation room) and active external (e.g. warming blanket) measures, should be utilised.

The use of tranexamic acid (TXA) as an antifibrinolytic therapy has become a standard of care for trauma patients with suspected haemorrhage who present within 3 h following trauma. TXA should also be given in some non-trauma situations such as in patients with postpartum haemorrhage and those bleeding following cardiac surgery [13]. The evidence for TXA use for gastrointestinal bleeding is weak and should generally be avoided. The use of high-dose intravenous TXA (4 g/24 h) may be associated with increased incidence of deep vein thrombosis, pulmonary embolism, and seizures [14].

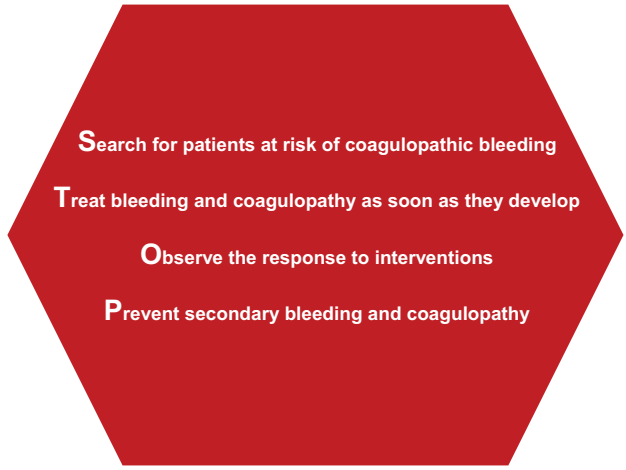

Fig. 49.2 The key tenets of the 'STOP the Bleeding' campaign. Adapted from Roissant et al. (2013), The STOP the bleeding campaign [15]

A group of European experts in surgery, critical care medicine, and haematology launched the 'STOP the Bleeding' campaign [15] in 2013 to improve awareness of trauma-induced coagulopathy. Their acronym is a useful summary of the key elements in managing bleeding trauma patients and can be generalised to the management of all patients with haemorrhagic shock (Fig. 49.2).

49.4.2 Haemodynamic Targets

The optimal blood pressure target for patients with hypotension and haemorrhagic shock is controversial. For trauma patients without evidence of traumatic brain injury (TBI), the current recommendation is to target a systolic blood pressure of 80–90 mmHg (mean arterial pressure 50–60 mmHg) until haemostasis has been achieved [16]. For those with a suspected severe TBI (i.e. GCS $\leq$ 8), resuscitation to a mean arterial pressure of $\geq$80 mmHg is recommended. Permissive hypotension as a component of 'damage control resuscitation' (DCR) has not been studied in any large randomised controlled studies but has still been adopted by many trauma guidelines [17]. Its role in the non-trauma setting is more uncertain, but it is still encouraged by some clinicians for the initial resuscitation of patients with ruptured AAA and massive upper gastrointestinal bleeding [18].

The role of vasopressor support has not been rigorously examined in haemorrhagic shock patients. Intense compensatory vasoconstriction may be increased by early use of intravenous vasopressors in haemorrhagic shock and precipitate end-organ ischaemia. However, in patients who are not responsive to fluids and haemostatic resuscitation, vasopressors may be necessary to maintain perfusion pressure [19]. Noradrenaline is the recommended first-line vasopressor agent. Adrenaline or dobutamine may be considered in patients with concomitant myocardial dysfunction.

49.4.3 Definitive Interventions

Early, definitive haemostasis reduces blood transfusion requirements and mortality for patients presenting with haemorrhagic shock from pathologies including pelvic fractures, ruptured AAA, and gastrointestinal bleeding [10]. Definitive care may include interventions such as endoscopy for upper gastrointestinal bleeding, angiography for embolisation of bleeding pelvic vessels, or surgical exploration (e.g. laparotomy or thoracotomy) for intra-abdominal or intrathoracic bleeding. There may be some conjecture in choice of intervention in unstable bleeding patients where the source remains uncertain. This is particularly significant in blunt trauma patients where prompt decisions need to be made regarding prioritising the most prominent bleeding anatomical site.

Damage control surgery is a widely adopted, staged surgical approach to control bleeding and contamination. Its use is well described in trauma, and it has a sound rationale in non-trauma haemorrhagic settings as well. Abbreviated surgical procedures such as ligation of bleeding vessels, application of temporary shunts, abdominal packing, splenectomy, or nephrectomy [20] may control bleeding without further exacerbating hypothermia, acidaemia, and coagulopathy. Limiting operation time to less than 90 min per intervention reduces these risks [15].

Following definitive intervention, patients with resolving haemorrhagic shock should be monitored closely for secondary bleeding, ongoing coagulopathy, and the sequelae of fluid over-resuscitation or prolonged shock state. Normalisation of lactate and base excess can be interpreted as markers of adequate resuscitation and haemostasis. A haemoglobin transfusion threshold of >7 g/dL is generally accepted for stable patients in the intensive care unit.

Take-Home Messages

- Haemorrhage is a preventable cause of death, and early recognition and treatment are vital to ensure survival
- Coagulopathy may occur when the coagulation system becomes overwhelmed and can be exacerbated by hypothermia and acidaemia (the 'lethal triad')
- There should be a low threshold to consider bleeding as the cause of shock in at-risk patients such as those with chronic liver disease, underlying coagulopathy, known vascular or gynaecological pathology, recent surgery, or trauma
- Lactate and base deficit can be quickly obtained from arterial blood gas analysis to monitor severity of the shock state and resuscitation response.
- Delays in activating a massive transfusion protocol are associated with increased risk of mortality for every minute delay in initial blood product arrival.
- Damage control surgery is a widely adopted, staged surgical approach to control bleeding and contamination.
- Patients with resolving haemorrhagic shock should be monitored closely for secondary bleeding, ongoing coagulopathy, and the sequelae of their shock state.

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Massive Haemothorax of Extremely Rare Cause: Learnings from an Unusual Case Report

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Contents

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Learning Objectives

- Management of an acute massive haemothorax
- Medical-surgical coordination of emergencies of vascular origin
- Importance of imaging studies
- Late complications of thoracic spine surgery

50.1 Introduction

Haemothoraces are a common entity (mainly of traumatic origin) and depending on their severity can be life-threatening. However, an iatrogenic haemothorax, although known as possible post-surgical complications of many thoracic surgeries, is a rare but potentially life-threatening entity. Scoliosis surgery is one of the surgeries where this complication is described, especially in the immediate postoperative period.

The placement of thoracic drains is usually sufficient for its treatment, although in some cases, the surgical alternative must be used, or in others, it may be modified depending on the findings of complementary tests and the patient's condition.

The following case presentation provides a very relevant learning experience for any physician involved in intensive care medicine due to its content on the management of sudden dyspnoea, comprehensive approach to haemothorax, therapeutic implications, and always remembering to consider the potentially fatal complications that may arise in the long term after any thoracic surgery.

Case Presentation

This is the case of an 18-year-old male of marfanoid appearance, weighing 45 kg, 165 cm tall, COVID-19 positive (predominantly asymptomatic), and with a history of surgical correction of scoliosis 9 months earlier with satisfactory postoperative outcome. He was taken to the emergency department after being reported for presenting, at rest and with no apparent trigger: sudden, intense, and stabbing dorsal pain, immediately followed by dyspnoea and, subsequently, syncope. Upon arrival at the hospital, he was conscious, oriented, and cooperative, with the following vital signs: afebrile tachypnoea of 24 breaths per minute with hypophonesis of the left hemithorax on auscultation, blood pressure of 60/40 mmHg, heart rate of 105 bpm, and $SatO_2$ 100% with nasal oxygen at 2 L per minute. Abdominal examination was unremarkable. There was no evidence of mucocutaneous pallor or other relevant semiological signs. Fluids were started with little improvement in blood pressure: 85/54 mmHg. Emergency venous blood gas analysis showed the following results: pH, 7.26; lactate, 3.5 mmol/L; haematocrit, 41%; and haemoglobin, 13.9 g/dL. It was decided to perform an urgent ultrasound scan and request a chest X-ray.

50.2 Investigations

While awaiting portable radiology, the FATE (Focus assessed transthoracic echocardiography) and E-FAST (the Extended Focused Assessment with Sonography in Trauma) protocols were performed, which revealed a large left pleural effusion, but no alterations in cardiac function. Next, a chest X-ray (Image 50.1a) showed radi-

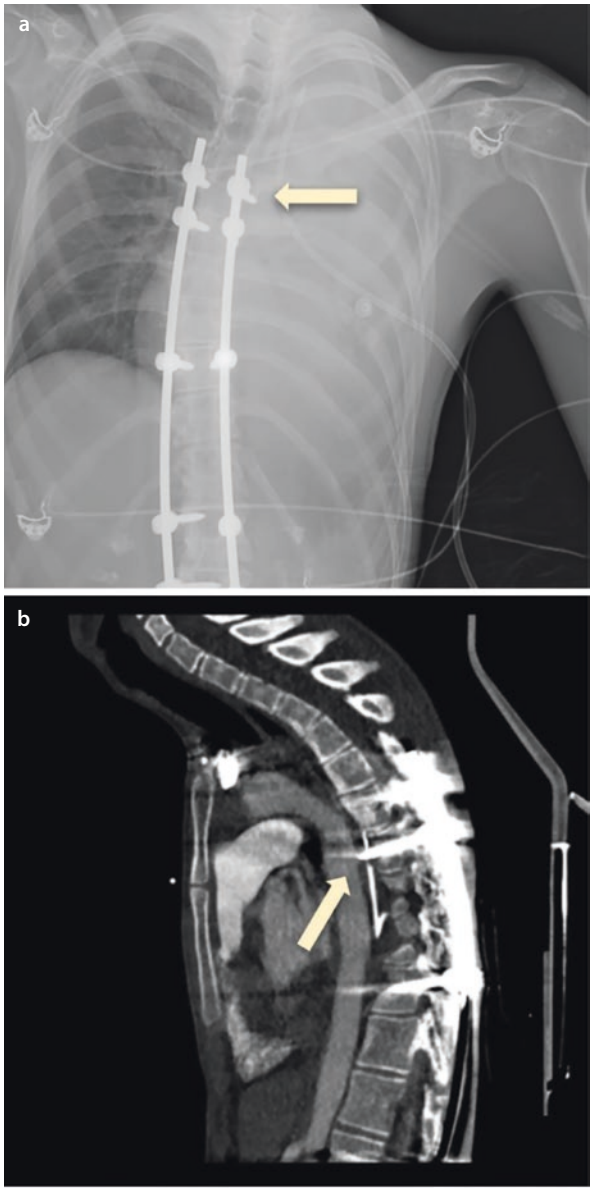

Image 50.1 (**a**) Radiopacity of the right hemithorax suggestive of haemothorax. (**b**) Compression of the tip of a screw of the thoracic spine fixation material (pedicle screw), which was in close contact with the posterior face of the descending thoracic aorta

opacity occupying the totality of the left hemithorax. In light of this finding, given the relative clinical stability of the patient and the maintenance of adequate oxygen saturation levels, it was decided to postpone the placement of a thoracic drain until a thoracic CT scan could be performed to provide information on the presence or absence of active bleeding, avoiding the placement of a 'blind' thoracic drain that would eliminate the potential haemostatic effect that the blood itself was having on a hypothetical bleeding point, hitherto unknown.

The CT scan showed deviation of the mediastinum to the right, with atelectasis of the left lung accompanied by the complete occupation of the hemithorax by fluid of different densities compatible with haemothorax at different stages. The CT scan also showed compression of the tip of a screw of the thoracic spine fixation material (pedicle screw), which was in close contact with the posterior face of the descending thoracic aorta (◘ Image 50.1b). Although continuity injury to the aortic wall was suspected at the tip of the transpedicular screw, the metal density partially artefacts the test results. No active bleeding was evident in the different phases of intravenous contrast administration. No other relevant findings were observed.

50.3 Differential Diagnosis

Given the presence of sudden dyspnoea accompanied by hypotension in an 18-year-old patient with no known medical history, the following differential diagnoses were established:

1. Acute pulmonary thromboembolism:
   (a) Compatible or probable because of sudden presentation of dyspnoea, hypotension, syncopal episode, and SARS-COV2 positivity, which is usually propitious for a procoagulant state. In addition, in young people with no history, the presence of congenital anticoagulation disorders cannot be ruled out
   (b) Not compatible or probable based on D-dimers of 1.4 μ/mL, maintaining oxygen saturations of 100% with the only nasal oxygen supply at 2 L per minute, which would be extremely rare in a pulmonary thromboembolism debuting with hypotension and syncope
   (c) Ruled out by biventricular function on echocardiography with no signs of right chamber overload and the absence of pulmonary artery repletion defects on CT angiography
2. Ischaemic, valvular, or pericardial cardiac pathology:
   (a) Compatible or probable based on the sudden presentation of dyspnoea and hypotension
   (b) Not compatible or unlikely based on no history of cardiac pathology. Electrocardiogram without alterations suggestive of ischaemia. Good distal perfusion on arrival
   (c) Ruled out by normal echocardiography and CT angiography findings
3. Worsening of his SARS-COV2 infection:
   (a) Compatible or probable based on the known diagnosis of SARS-COV2 and the presence of dyspnoea
   (b) Not compatible or unlikely based on asymmetric auscultation, sudden presentation, and minimal oxygen requirements to maintain saturations of 100%

   (c) Ruled out because of evidence of left pleural effusion and CT findings
4. Thoracic aortic dissection
   (a) Compatible or probable based on marfanoid habitus and sudden interscapular chest pain with hypotension and syncope
   (b) Not compatible or probable based on bilateral symmetrical pulses
   (c) Ruled out by CT scan results
5. Pneumothorax
   (a) Compatible or probable based on described cases of spontaneous pneumothorax in young males with a marfanoid appearance
   (b) Ruled out by imaging test results
6. Other: As the patient was evaluated that same year by the anaesthesia department, he had a medical history that allowed us to verify the absence of a known history of consumption of toxic substances, normal family, and social context, acquired or hereditary coagulopathies, neoplasms, and soft tissue tumours associated with haemothorax (sarcomas or angiosarcomas). Therefore, the following were immediately ruled out or at least considered highly unlikely: traumatic haemothorax or pneumothorax, anxiety attack, acute psychiatric pathology, exacerbation of COPD, anaphylactic shock (without known allergies and absence of inspiratory stridor), neurological diseases, or metabolic disorders such as diabetic acidosis or hyperthyroidism.

50.4 Treatment

Once the absence of active bleeding was confirmed, a thoracic drain was placed, achieving normalisation of the heart rate and respiratory rate. After placement of the drain, there was no anaemisation in relation to the admission parameters. The case was discussed with the thoracic surgery, vascular surgery, and traumatology departments. Specialists from these departments proceeded to perform joint surgery on day +1, in which an endovascular prosthesis (◘ Image 50.2) was placed in the descending thoracic aorta, with distal and proximal ballooning but not at the level of the fixation screw due to the risk of rupture of the endoprosthesis. The thoracic spine fixation material was then partially removed (◘ Image 50.2), including the perforating screw. Once removed, the indemnity of the endoprosthesis was verified by intrasurgical arteriography. In the surgical report, the aorta is described as ‘very fragile and soft’. During the surgical procedure, the patient presented significant bleeding that required the transfusion of 4 packed red blood cell, platelets, fibrinogen, and prothrombin complex.

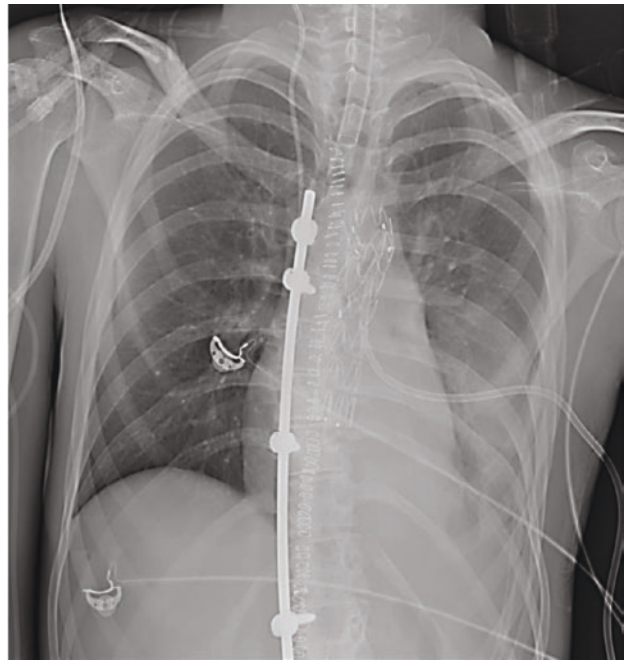

Image 50.2 Image corresponding to the postoperative situation of the patient showing the partial removal of the fixation material, the topographical situation of the endoprosthesis and the resolution of the haemothorax with the placement of a thoracic drain

50.5 Evolution, Outcome, and Follow-Up

After the intervention, the patient was extubated on day +3 of admission. A few hours later, he developed a new episode of respiratory difficulty accompanied by hypoventilation in the left hemithorax, and atelectasis was observed on chest X-ray. A 'toilette' was performed with aspiration of secretions with fibrobronchoscopy and oxygen supply with high-flow nasal oxygen with unsatisfactory results. On day +4, 24 h after extubation, the patient was reintubated. Rapid and marked improvement in the respiratory and ventilatory profile, progressing to extubation again 48 h later (day +6 of admission), which again failed under the same conditions of left atelectasis. Once again, the patient showed a rapid and satisfactory evolution under mechanical ventilation, both in terms of gasometric profile and ventilatory mechanics. For this reason, on day +8 of admission, he was extubated again, with another failure that warranted a third reintubation. At this point in the clinical session, the possibility of collapse of the airway of the left main bronchus due to the vascular prosthesis was discussed, and it was decided to perform fibrobronchoscopy without positive pressure from the respirator, which showed a dynamic collapse of 50%. A new CT scan was performed, confirming the findings.

The case was discussed again with the pulmonology and thoracic surgery departments, and the placement of an endobronchial prosthesis was ruled out in a joint session due to the risk of bronchial necrosis or removal of the aortic endovascular prosthesis. Finally, it was decided by consensus to proceed with tracheostomy on day +9 of admission and to maintain prolonged ventilation with positive pressure mechanical ventilation until stabilisation of the bronchial tree. Following tracheotomy, sedation was withdrawn, and the patient was maintained on pressure support, which was initially well tolerated. However, there were many difficulties in the following weeks for intermittent disconnections due to the appearance of complications related to the withdrawal of positive pressure: abundant secretions from the left lung, atelectasis, and difficult to manage cough, requiring bronchoscopies for 'bronchial toilette'. When bronchial stability secondary to the decrease in dynamic bronchial collapse allowed it, progressive disconnections, and the start of decannulation were initiated, made difficult by vocal cord paralysis, which led to basal aspirations and episodes of coughing that were difficult to control. This situation required a percutaneous endoscopic gastrostomy, maintenance of the tracheostomy, and treatment with amitriptyline as a secretion reducer.

By means of respiratory physiotherapy and vocal rehabilitation, glottic closure was finally recovered, allowing him to be discharged from the intensive care unit after 104 days of admission, decannulated, tolerating an oral diet, without new episodes of atelectasis and without evidence of dynamic collapse of the left bronchus.

50.6 Discussion

The injuries secondary to scoliosis surgery have been described for decades, including pulmonary, neurological, osteoarticular, vascular, and other types of injuries [1, 2]. Although infrequent, cases of aortic perforation by fixation screws have been reported. However, as a long-term complication of aortic perforation by fixation screws, probably less than a dozen cases are known, including those described by Wegener or Zerati [3, 4].

Although intraoperative radiographic control to confirm placement of the fixation screws is widespread, some series of postoperative CT scans report up to 15% of cases of malposition [5].

In the case presented, endovascular repair of the aorta and removal of the fixation screw were performed in the same surgical procedure. However, in the literature, some surgical teams have opted for endovascular treatment with screw removal at a second surgical time [6], while in other cases, aortic repair was performed without screw removal [4].

This case contributes further data to the literature on a very rare but potentially life-threatening entity. The radiological, medical, and surgical approach, including the subsequent complications, provide a special learning value.

Take-Home Messages

- In some cases of massive haemothorax, if the patient remains respiratory stable and with tolerable hypotension, it may be advisable to perform a thoracic CT scan before placing a drain. In this way, active bleeding can be ruled out, and the haemostasis that contains it under control can be lost by placing a drain that causes the chest to lose its watertightness.
- In a young patient with sudden-onset interscapular pain, spontaneous pneumothorax, aortic dissection, cardiac pathology, and pulmonary thromboembolism should be among the top differential diagnoses, even if the patient has a recent history of spinal surgery as in the case described.
- For every physician dedicated to intensive care medicine, the fluent use of ultrasound is a skill to be acquired during training. The diagnostic speed, the availability, and the wealth of information it provides can help to manage a clinical case correctly.
- A close multidisciplinary relationship and constant communication is essential in complex cases.
- Patients like the one presented in this report teach us that cases sometimes do not end when we think they will. Although it is extremely rare for a series of complications such as those described to occur consecutively, the great final lesson of this case is to take each of them and digest them to have them in our pool of knowledge along with their implications.

Summary

This is the case of an 18-year-old male with a history of surgical correction of scoliosis 9 months earlier with satisfactory postoperative controls. He was taken to the emergency department presenting sudden dorsal pain and dyspnoea. In the hospital, hypophonesis was found on the left hemithorax. It was decided to perform an urgent ultrasound, which revealed a large left pleural effusion. Then, a CT scan showed deviation of the mediastinum to the right with atelectasis of the left lung accompanied by complete occupation of the hemithorax by haemothorax at different stages. The CT scan also showed compression of the tip of a screw of the thoracic spine fixation material, which was in close contact with the posterior face of the descending thoracic aorta. Thoracic drain was placed, achieving normalisation of the heart rate and respiratory rate. The case was discussed with the thoracic surgery, vascular surgery, and traumatology departments. Specialists from these departments proceeded to perform joint surgery on day +1, in which an endovascular prosthesis was placed in the descending thoracic aorta and the thoracic spine fixation material was then partially removed. After many complications and difficulties in weaning from mechanical ventilation related to atelectasis of the left lung, it was determined that there was a dynamic collapse of the left main bronchus of up to 50% due to the vascular endoprosthesis placed. The idea of stent removal or placement of an endobronchial stent was ruled out, deciding on a conservative approach. By means of respiratory physiotherapy and vocal rehabilitation, glottic closure was finally recovered, allowing him to be discharged from the intensive care unit after 104 days of admission, decannulated, tolerating oral diet, without new episodes of atelectasis, and without evidence of dynamic collapse of the left bronchus.

Acknowledgements We would like to thank the Radiology Department of the Hospital Universitario de Salamanca for providing the images and the Vascular Surgery, Anaesthesiology, Traumatology, Thoracic Surgery, Pneumology, and Rehabilitation Departments for all the technical support during the patient's admission. Finally, thanks to the patient and his immediate family who gave their consent for the publication of this case to be useful at a pedagogical level for any intensivist in the world who can learn from this case.

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Case Report: An Unusual Cause of Syncope

Momna Ehsan and Richard Lowsby

Contents

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Learning Objectives

- Learning objective 1. To review the causes of syncope and abdominal pain in a young patient
- Learning objective 2: To describe the aetiology of splenic rupture associated with viral illness

51.1 Introduction

Splenic rupture is associated with a high mortality if diagnosis is delayed, and trauma remains the predominant cause. Atraumatic splenic rupture is rare, but its prompt diagnosis is essential for good outcomes. It may not be considered in the differential diagnosis of abdominal pain and could lead to significant haemodynamic compromise and mortality.

Infectious mononucleosis can cause splenomegaly, and about 0.5% of patients develop rupture [1]. With the emergence of the current pandemic, several cases have been reported where rupture is attributed to SARS-CoV-2 infection [2, 3]. We describe a case that tested positive for both viral infections.

Case Presentation

An 18-year-old female with no previously diagnosed medical conditions presented to the Emergency Department (ED) with a syncopal episode upon getting up from bed. Prior to this, she reported feeling unwell with sore throat, and a home lateral flow test had been positive for SARS-Cov-2. On presentation to ED, she complained of nausea with intermittent epigastric pain of severe intensity. She denied any history of trauma, diarrhoea, fever, urinary or respiratory symptoms.

She was not on any regular medications and lived with her parents, and there was no known family history of significant medical conditions.

On initial assessment in ED, she was pale and found to be profoundly hypotensive with a BP of 70/35 mmHg and tachycardic with a heart rate of 104/min. Her oxygen saturations were 99% on room air with a respiratory rate of 14/min. On examination, she had palpable cervical lymphadenopathy, and her chest was clear. Her abdomen was soft with mild central tenderness. The neurological examination was unremarkable.

51.2 Investigations

Her initial blood test results are set out in Table 51.1. Analysis of her full blood count revealed anaemia (Hb, 92 g/L) with elevated total leukocyte count (20.6×10^9/L) and lymphocytosis. Atypical mononuclear cells were demonstrated on blood film. In

Table 51.1 Initial blood results

Haemoglobin (Hb)	92	130–180 g/L
WCC (TLC)	20.6	4–11 × 10^9/L
Platelet count	228	150–450 × 10^9/L
Haematocrit	0.281	0.400–0.520 L/L
Neutrophils	9.42	1.70–7.50 × 10^9/L
Lymphocytes	8.82	1.0–4.0 × 10^9/L
Basophils	0.09	0.0–0.1 × 10^9/L
Eosinophils	0.03	0.04–0.40 × 10^9/L
Monocytes	2.19	0.20–0.80 × 10^9/L
Sodium	138	133–146 mmol/L
Potassium	4.8	3.5–5.3 mmol/L
Urea	5.3	2.5–7.8 mmol/L
Creatinine	113	60–120 μmol/L
Alanine transaminase	277	10–60 IU/L
Alkaline phosphatase	135	30–130 IU/L

view of this, a monospot test was performed and was found to be positive, raising suspicion of co-existent Epstein–Barr Virus (EBV) infection. The pregnancy test was negative.

Fluid resuscitation commenced, and referral made to the critical care team. In view of her haemodynamic status and abdominal symptoms, CT imaging of her abdomen was organised.

51.3 Differential Diagnosis

Based on the clinical presentation of syncope and abdominal discomfort, differential diagnoses included sepsis related to COVID-19, Addisonian crisis, intra-abdominal sepsis, pancreatitis, and ectopic pregnancy. With a positive monospot test, splenic rupture was considered as a rare complication.

The CT scan revealed a large heterogeneous perisplenic hematoma with a size of 15 × 11 cm associated with a moderate degree of hemoperitoneum. The absence of intrasplenic hematoma and a normal-sized spleen was noted (Fig. 51.1).

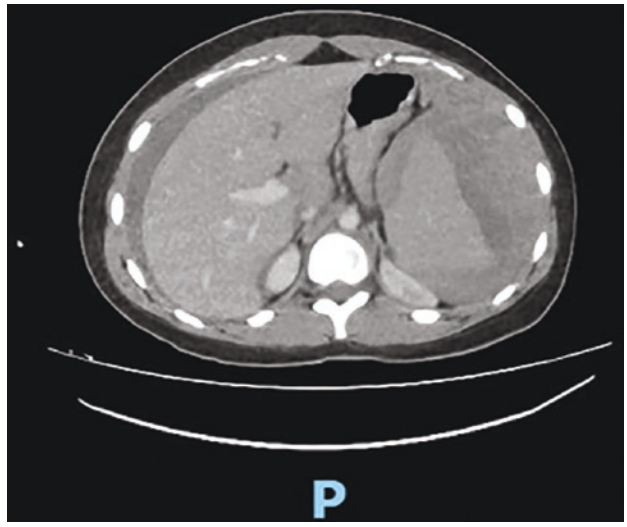

Fig. 51.1 Cross-sectional imaging of the abdomen demonstrating perisplenic haematoma and hemoperitoneum

51.4 Treatment

She was initially resuscitated with fluids and received intravenous tranexamic acid, hydrocortisone, and antibiotics for sepsis coverage. Upon radiological confirmation of perisplenic haematoma, surgical input was requested, and the decision was made to perform an urgent splenectomy. Upon exploration in theatre, the patient was found to have a large volume of hemoperitoneum and a spleen ruptured at several sites. Blood loss was estimated at 3 L. The rest of the abdominal viscera were healthy, and no accessory spleen was appreciated. During the procedure, 3 units of red blood cells and 4 units of fresh frozen plasma were transfused.

51.5 Evolution, Outcome, and Follow-Up

After surgical treatment, the patient was transferred to the critical care covid-isolation-unit and was extubated within 12 h of surgery. Despite being SARS-Cov-2 positive, she had no features of pneumonitis. She made a good recovery and was discharged home on day 10. During her admission, she received post-splenectomy immunizations and was discharged on long-term penicillin prophylaxis.

51.6 Discussion

Splenic rupture is a life-threatening condition, and its diagnosis can be challenging in the absence of chest or abdominal trauma. Incidence has been reported at 0.1%–0.5%, and common causes include malignancy (e.g., lymphoma), inflammatory con-

ditions (e.g., sarcoidosis), and infectious diseases (e.g., malaria, EBV, dengue). Spontaneous splenic rupture is rare in young adults; it is mostly attributed to EBV-associated infectious mononucleosis. With the evolution of the pandemic, cases of splenic rupture have also been seen in association with COVID-19 [3, 4].

Although cases have been reported in all age groups, infectious mononucleosis most commonly affects people aged 15–24 years. Spontaneous splenic rupture, a well-known complication of infectious mononucleosis, affects males more commonly than females. With this infection, mononuclear cells proliferate within lymphoid tissues, e.g., spleen causing splenomegaly and thus more prone to rupture. The mean time between the onset of symptoms and splenic rupture is about 14 days with a maximum of 8 weeks [5]. Quite commonly, young adults with infectious mononucleosis are advised to avoid contact sports and vigorous activity for at least 4–8 weeks. In this case, however, splenic rupture occurred within a week of symptom onset.

The precise mechanism of splenic rupture in patients affected with COVID-19 remains unclear. Recently, a study has shown that SARS-CoV-2 virus can infect the spleen and lymph nodes due to the presence of specific receptors on macrophages and consequently leads to lymphocytopenia and tissue damage [6]. In addition, hypercoagulable state can lead to microvascular thrombosis and splenic necrosis.

The case presented is uncommon in nature as it had two potential viral causes of splenic rupture, i.e., glandular fever and SARS-CoV-2 infection. It was noticed that splenic size was normal, unlike the splenomegaly commonly seen with infectious mononucleosis, and contained multiple lacerations, which correlates with other case reports of SARS-CoV-2 infection. We postulate that both viruses had an additive effect on the spleen increasing the risk of rupture.

In this case, simple yet important investigations like raised white cell count/WCC (lymphocytosis) and a blood film with atypical lymphocytes raised the suspicion of EBV infection. The positive monospot test, in combination with the clinical picture of collapse and intermittent abdominal pain, led to the consideration of a diagnosis of splenic rupture. Commonly described clinical features including peritonism and Kehr's sign (acute shoulder tip pain due to blood in the peritoneal cavity) were absent in this instance, making the diagnosis more challenging and potentially easy to miss. This emphasizes the importance of maintaining a high index of suspicion for rare complications of EBV infection and of novel presentations with COVID-19.

Take-Home Messages

- In young patients with syncope: Remember spleen.
- Attention to detail: If WCC is raised, look for the differential count.
- COVID-19: A possible cause of spontaneous splenic rupture.

Summary

We describe a case of a young patient who presented with syncope and was found to have an atraumatic rupture of spleen. She was tested positive for both EBV and SARS-CoV-2 infection. After having an emergency splenectomy, she recovered well and was discharged home on penicillin prophylaxis.

Acknowledgements We thank the patient for giving her consent to write the report.

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Blood Transfusion-Triggered Posterior Reversible Encephalopathy Syndrome

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Contents

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Learning Objectives

- Diagnosis of PRES and radiological findings
- Etiology and pathophysiology of PRES
- Management of PRES
- Awareness of transfusion-related PRES and prevention strategies

52.1 Introduction

Posterior reversible encephalopathy syndrome (PRES) is a rare neurological condition occurring due to the inability of the brain circulation to autoregulate in response to acute blood pressure changes. Hyperperfusion along with blood–brain barrier disruption resulting in vasogenic edema (usually without infarction) and mostly in the bilateral parieto-occipital region are the typical features of this condition [1]. It presents clinically with seizures, headache, loss of consciousness, visual disturbances, and focal neurologic deficits. Computed tomography (CT) and magnetic resonance imaging (MRI) studies show extensive bilateral white-matter abnormalities, which are suggestive of edema in the posterior regions of the cerebral hemispheres. Other areas of the brain may also be involved.

Case Presentation

We report a case of a 32-year-old woman with no past medical history who presented to an outside hospital with abdominal pain and distension. She was diagnosed with a large pelvic mass showing cystic and solid densities with severe anemia (hemoglobin, 2 g/dl). She was transfused with six units of packed red blood cells (PRBC) for 2 days. The patient developed an episode of generalized seizures and, hence, was referred to our hospital. She had one more episode of seizure upon arrival at our hospital and was intubated for airway protection and was treated with antiepileptic drugs.

52.2 Investigations

MRI of the brain showed multifocal cortical (gyriform) and subcortical FLAIR and T2 hyperintensities in bilateral frontal, parietal, and occipital region and corona radiata consistent with PRES (Figs. 52.1 and 52.2). After blood transfusion, the hemoglobin level was 6 g/dL, and a workup for underlying malignancies was performed; however, both CA19-9 and CEA 125 were negative. Cerebrospinal fluid analysis (CSF) revealed normal protein and glucose levels without pleocytosis. CSF workups for paraneoplastic syndrome and autoimmune encephalitis were negative. Transthoracic echocardiography showed moderate left ventricular dysfunction.

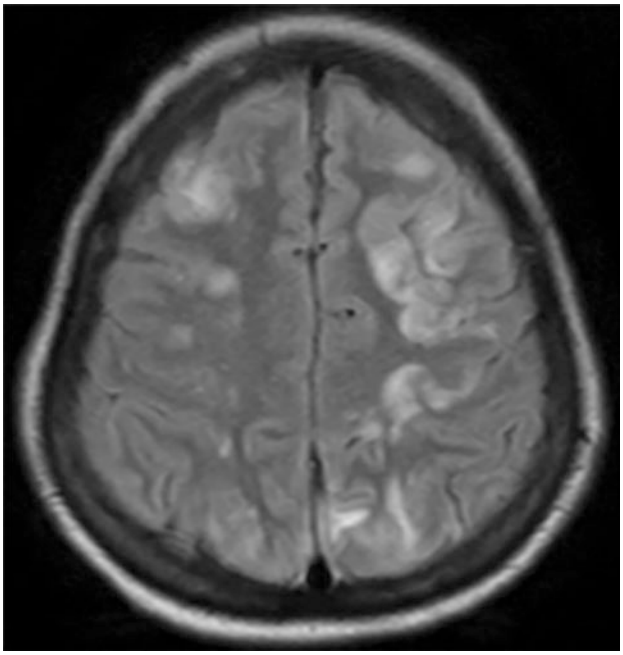


Fig. 52.1 MRI brain FLAIR-weighted images show hyperintensities in the left more than the right frontoparietal region and the occipital region

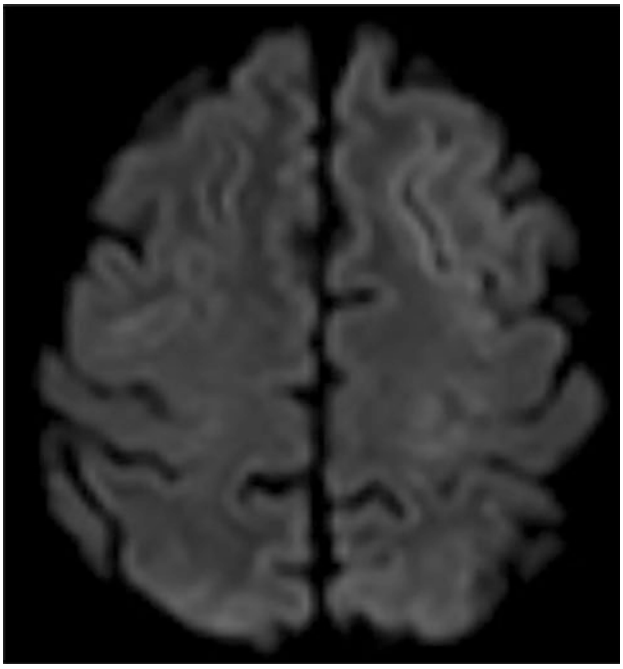


Fig. 52.2 MRI DWI showing subtle diffusion restriction in the left frontoparietal region

52.3 Differential Diagnosis

Differential diagnoses for our case included meningoencephalitis, posterior reversible encephalopathy syndrome, anemia with cortical vein thrombosis, autoimmune encephalitis, paraneoplastic syndrome, hypertensive emergency, and intracranial metastasis with gynecological malignancy.

52.4 Treatment

She was intubated for airway protection and was treated with antiepileptic drugs. She was transfused with one more unit of PRBC. Her sensorium gradually improved, and she was weaned off the ventilator and was transferred to the ward.

52.5 Evolution, Outcome, and Follow-Up

After stabilization, she underwent laparotomy and was found to have multiple degenerated fibroids, and myomectomy was done.

52.6 Discussion

Posterior reversible encephalopathy syndrome is an acute neurological condition characterized by a spectrum of neurological and radiological features. It could result from posterior cerebral arterial circulation, and dysfunction, inducing cerebral vasogenic edema and/or vascular endothelial damage.

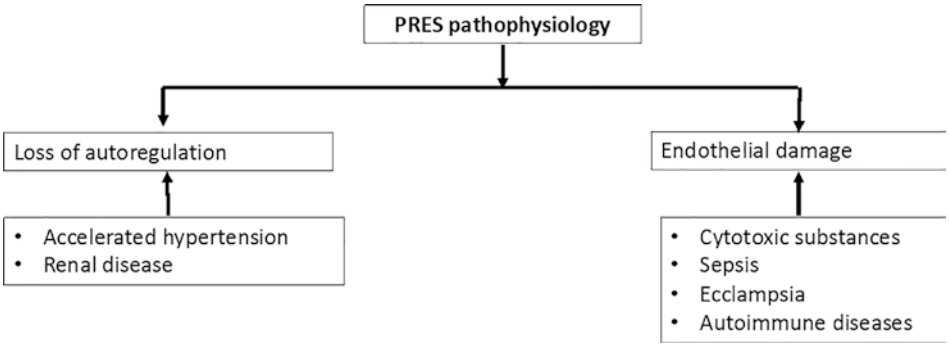
MRI demonstrates bilateral cortico-subcortical T_2 and FLAIR confluent hyperintensities, predominantly in the watershed zones of parietal and ► occipital lobes (95%) and lesser in the ► frontal lobes, ► temporal lobes, brain stem, or in the cerebellum [2]. MRI brain diffusion-weighted imaging demonstrates iso-/hypointense areas, suggesting the possibility of vasogenic edema ranging from mild to severe intensity. Involvement of the classic parieto-occipital region is seen in only 59% of the patients.

Clinical symptoms might develop over hours to days and can range from mild somnolence to coma or from headache to visual disturbance and seizures (◘ Table 52.1) [3].

◘ **Table 52.1** Clinical features and their incidence of posterior reversible encephalopathy syndrome

Clinical features
Seizures, 74% (18% with status epilepticus)
Encephalopathy, 28%
Headache, 26%
Visual disturbances, 20%

Table 52.2 Flowchart depicting pathophysiology of PRES



Two major hypotheses have been described to explain the pathophysiology of PRES (Table 52.2). One is loss of autoregulation due to blood pressure fluctuations leading to cerebral hyperperfusion, which in turn increases capillary leakage and vasogenic edema.

Another hypothesis is endothelial damage caused by endogenous or exogenous agents secondary to preeclampsia, sepsis, cytotoxic agents, and chemotherapy medications. This will lead to vascular leakage and cerebral edema.

Major risk factors for PRES are hypertension, eclampsia, sepsis, autoimmune disease, chemotherapy, transplantation, and renal failure [4]. Delayed diagnosis may cause irreversible damage in the form of ischemia or bleeding and may carry a high mortality rate; hence, it is important to diagnose early and treat the risk factors such as controlling blood pressure, withdrawal of the offending drug, etc. Blood transfusion-related PRES even though very rare has been reported in the literature, and most of them are gynecological cases in adult females. Most of the cases were related to uterine fibroids. The average change in hemoglobin was 6.21 g/dL [5]. Chronic severe anemia can be a predisposing factor. Anemia may lead to hypoxemia in the brain, which may cause endothelial dysfunction and damage to the blood-brain barrier. The other possibility would be multiple blood transfusions causing activation of complement-mediated (immune complex) activation of T cells, resulting in endothelial damage leading to PRES. Multiple blood transfusions may cause a rapid increase in total blood volume, which further leads to cerebral blood flow overload. Abrupt cerebral hyperperfusion exceeding the capacity of autoregulation of cerebral circulation results in vasogenic edema found in PRES.

Our patient was normotensive and had no major risk factors. She received a rapid blood transfusion over 2 days. Massive blood transfusion causing increased blood volume might have led to PRES. We suggest slow blood transfusion in patients with chronic anemia to prevent the development of PRES.

Take-Home Messages

- Workup of seizures
- Diagnosis of PRES
- Awareness of transfusion-related PRES
- Diagnosis of transfusion-related PRES
- Management of chronic anemia

Summary

A 32-year-old female patient presented to an outside hospital with abdominal pain and distension. She was diagnosed with a large pelvic mass and severe anemia. She was transfused with six units of packed red blood cells (PRBC) for 2 days. She developed an episode of generalized seizures and, hence, was referred to our hospital. She had one more episode of seizure upon arrival at our hospital. She was intubated for airway protection and was treated with antiepileptic drugs. The patient had a workup that included MRI, blood tests, and CSF analysis. The patient was transfused with one more unit of PRBC. The patient's condition improved clinically and was extubated. The patient was diagnosed with transfusion-related PRES based on the reports and the exclusion of other common etiologies. After stabilization, she underwent laparotomy where she was found to have multiple degenerated fibroids. Multiple blood transfusions may cause a rapid increase in the total blood volume, which further leads to cerebral blood flow overload. Abrupt cerebral hyperperfusion exceeding the capacity of autoregulation of the cerebral circulation results in vasogenic edema found in PRES. We suggest slow blood transfusion in patients with chronic anemia to prevent PRES development.

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The Best Clinical Cases in Severe Endocrine and Metabolic Disorders

Contents

Endocrine and Metabolic Disorders in the ICU

Mehmet Yildirim and Gaetano Scaramuzzo

Contents

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Learning Objectives

- Understand the importance of endocrine and metabolic disorders in intensive care.
- Describe the clinical features, diagnostic workup, and complications of diabetes, acute porphyria, and cyanide poisoning in critically ill patients.
- Learn the current management strategies of diabetes acute complications, acute porphyria, and cyanide poisoning.

53.1 Diabetes in the ICU

Diabetes mellitus (DM) type 1 is caused by an autoimmune destruction of pancreatic B-cell and the consequent hypoinsulinemia; type 2 diabetes, which is the most frequent in the world, is caused instead by insulin intolerance and relative insulin deficiency. Diabetes acute complications requiring ICU admission are related to hypoglycemia and/or hyperglycemia. Usually, diabetic patients are admitted to the ICU in three different conditions: hyperglycemic crises, hypoglycemia, or metformin associated lactic acidosis (MALA).

- **Hyperglycemic crises:** Hyperglycemia crises account for more than 90% of complication of diabetic patients and can present in two clinical syndromes, i.e., the diabetic ketoacidosis (DKA) and the hyperosmolar hyperglycemic nonketotic (HHNK). While DKA is usually a complication of type 1 DM, the second is classically a complication of type 2 DM.

  DKA*:* Insulin absolute deficiency is associated to an increase of counterregulatory hormones that increase gluconeogenesis and glycogenolysis. The absence of insulin determines an increase of lipolysis and free fatty acid release, which determines hyperglycemia and ketosis.

  Ketone bodies (KB) are formed in the mitochondrial matrix through the path of ketogenesis from fatty acids and/or ketogenic amino acids. KB are released also in nondiabetic persons, in case of low carbs states or prolonged fasting, and represent an additional energetic substrate for the brain tissue. In DKA, the concentration of ketones is above normal (>3 mMol/L) [1], and patients are usually affected by type 1 diabetes.

  Higher levels of glucose in the blood determine glycosuria and osmotic diuresis, hypovolemia, and decreased renal function. The KB are produced in the liver through the oxidation of fatty acids and determine a metabolic organic acidosis. The increase of KB may also produce consciousness alteration and abdominal pain. Stressful situations like infections, inadequate therapy, or new onset of diabetes may characterize patients affected by DKA.

  The severe osmotic diuresis determines high water loss and electrolyte imbalance such as hypo-hypernatremia (for glucagon and for the osmotic diuresis) and hyper-hypokalemia (due to vomiting and secondary hyperaldosteronism).
- ***HHNK****:* In HHNK, insulin is not abolished but remains low. Glucose is therefore used at low rates and lipolysis is higher but not as in DKA. In this context, we have severe hyperglycemia with osmotic diuresis and dehydration but no acidosis or KB increase [2]. Nevertheless, if dehydration persists, water losses may determine hypovolemic shock and lactate increase for cellular hypoperfusion and determine metabolic acidosis through hyperlacticemia.

Clinical Presentation and Diagnosis

The patient affected by a hyperglycemia crisis is usually hypovolemic and has a recent history of polyuria, polydipsia (may be absent in the elderly), nausea/vomiting, abdominal pain, and weakness. A history of diabetes may suggest the diagnosis. Signs of dehydration (skin, oliguria, low central venous pressure, tachycardia) may be found.

Hypernatremia may be also present with its clinical sequelae (neurological alterations, coma, seizures) because of hypovolemia. Acid breath ("ketotic breath") is specific and may be useful for the diagnosis which is confirmed by the laboratory findings of hyperglycemia (>250 mL/dL), metabolic acidosis, and ketonemia (in case of DKA).

Since KB consume bicarbonate, DKA is characterized by an increased anion gap ($Na^+ - [Cl^- + HCO_3^-] > 12$ mEq/L). Low albumin levels may present and may determine an altered AG calculation, and a corrected anion gap should be calculated as cAG (mEq/L) = AG + 0.25 (40—actual Alb) [3]. Metabolic acidosis is usually absent in HHNK patients, but hyperlacticemia may determine lactic metabolic acidosis.

The objectivation of elevated KB in the serum (hyper*ketonemia*) may help with the diagnosis of DKA, but it's time-consuming and requires resources. A quick evaluation of the ketonuria (increased KB in the urines) may provide a good surrogate for the diagnosis. Dipsticks for KB urine evaluation are only sensitive to acetoacetate and acetone and therefore may provide false negatives in some conditions.

Electrolyte disorders may be present. Natremia can be high or even low in case of hyperglycemia for dilution due to cellular dehydration; the correct natremia (cNa) need to be therefore calculated considering glycemia.

Hypernatremia may characterize the advanced phases of HHNK due to severe dehydration. Other laboratory findings may be a specific troponin I elevation, hyperamylasemia, hyperlipasemia, and laboratory findings suggestive of impaired renal function.

53.2 Management

The management of hyperglycemic crises is based on the following:

1. **Fluid replacement**: must be started as soon as possible to replace the urinary loss. The fluidic intervention may reduce per se ketonemia and hyperglycemia by dilution and increased cardiac output and organ perfusion. The mean fluid depletion at diagnosis is 6–7 L in adults with DKA, and a reintegration of 1–1.5 L in the first 2 h may be appropriate. Balanced crystalloid infusion can avoid the development of hyperchloremic metabolic acidosis due to saline infusion and must be therefore preferred. The volume loss in HHNK is usually even higher. In this case, the type of fluid needed and the amount must be in case based on the patient characteristics and on biological monitoring. The correction of hyperosmolarity must be slow, not exceeding 3–5 mOsm/L/h.
2. **Correction of electrolyte abnormalities:** Potassium, phosphates, and sodium levels may be altered. Although generally hyperkalemia is present at ICU admission, hypokalemia develops during the treatment, also for the K+ transmembrane shift

due to insulin infusion. Insulin infusion must be therefore delayed unless K+ levels are restored. In case of hyperkalemia with no other alteration, considering the natural evolution toward hypokalemia, K should be only monitored in the next 1–2 h.

3. **Correction of hyperglycemia:** Insulin therapy using ultrarapid insulin intravenously should be started only after restoring the vascular volume and correcting hypokalemia [1]. Once levels of 200 mg/dL for DKA and 300 mg/dL for HHNK are reached, insulin infusion must be reduced, and sugar intake should be started to maintain a glucose level between 150 and 200 mg/dL and avoid hypoglycemia.
4. **Alkalinization:** Addition of bicarbonate in DKA is recommended only in case of severe acidosis (pH <6.9). Nevertheless, an adequate fluidic therapy may stop the process of KB production, and therefore the acidification process allows normal pH restoration without external bicarbonate infusion. Until now, no definitive effect on long-term patient's centered outcome has been demonstrated, and therefore the bicarbonate infusion must be discussed on a case-by-case basis.

53.2.1 Metformin Associated Lactic Acidosis (MALA)

Metformin is the most used drug for type 2 diabetes treatment and allows to control glycemia and prevent the complications of diabetes by reducing insulin resistance. Metformin intoxication may determine lactic acidosis by an inhibition of mitochondrial respiration and an increase of anaerobic metabolism and therefore lactic acid production [4]. Moreover, an increase of glycolysis may also increase the lactate production, which is therefore not associated to an oxygen deficit but to its use (type B lactic acidosis). If hypoxia is present, both pathways can lead to lactic acidosis. This syndrome takes the name of MALA.

Metformin accumulation may be related to an increased assumption and reduced excretion (dehydration, hypovolemia, worsening renal function). Although the clinical symptoms of MALA are not specific (e.g., weakness, nausea, vomiting, hypothermia, abdominal pain), the pharmacological history and the presence of metabolic lactic acidosis (pH < 7.35 + lactates > 5 mMol/L) should orientate the diagnosis [5].

In case of renal dysfunction, renal replacement therapy (RRT) is needed to support renal function and may help to accelerate metformin elimination. Metformin levels reduce more rapidly during RRT despite no trial showing a survival benefit of RRT until now in MALA patients [5]. Theoretically, since metformin is a small molecule, intermittent hemodialysis is commonly recommended initially, but since metformin may accumulate, redistribution may happen and additional RRT sessions may be required. Continuous renal replacement therapy (CRRT) may be therefore considered if hemodialysis is unavailable or if the patient is hemodynamically unstable.

53.2.2 Hypoglycemia

Hypoglycemia in diabetes is usually a complication of diabetic treatment and can affect both type 1 and type 2 patients treated with insulin or oral antidiabetic agents.

While mild hypoglycemia may be treated by the patient using the oral route, severe hypoglycemia may need intervention.

Since patients affected by type 1 DM have an altered insulin/glucagon secretion, hypoglycemia does not effectively stimulate glucagon release, and patients may present hypoglycemia with signs of dysautonomia. Diabetic autonomic neuropathy is characterized by a high adrenergic response [6] resulting in tachycardia, anxiety, palpitation, and sweating. Hypoglycemic encephalopathy may also be present with coma, seizures, or cognitive dysfunction.

In case of mild hypoglycemia, the use of food with simple carbohydrates may be sufficient to alleviate symptoms. In severe cases, parenteral administration may be needed, with a glucose solution. A strict monitoring during time is necessary to avoid hypoglycemia recurrences.

53.3 Porphyria

53.3.1 Introduction and Pathophysiology

Heme is primarily synthesized in the liver requiring cytochrome P450 (CYPs). As the prosthetic group of numerous hemoproteins such as hemoglobin, myoglobin, respiratory cytochromes, cytochrome P450 (CYPs), and nitric oxide synthase, heme is essential for all functions and cells [7]. Porphyrias are a group of eight panethnic rare inherited metabolic disorders of heme biosynthesis which has eight steps (Fig. 53.1). Porphyrias have a wide variety of clinical manifestations ranging from mild diseases to critical illness. However, all of them are nonspecific and make the diagnosis challenging and often delayed. Patients with acute attacks of porphyrias usually require hospitalization, and many who presented with acute respiratory failure or central nervous system disorders need intensive care admission. Early diagnosis and appropriate management are essential for these patients [8].

53.3.2 Presentation

Classically porphyrias are classified as hepatic and erythropoietic according to localization of the enzyme defect. But, clinically they are divided into three groups: cutaneous, acute, or mixed. Cutaneous porphyrias are presented with skin lesions such as bullae and blisters due to dermal photosensitivity, while acute porphyrias are usually associated with high concentrations of the precursors of porphyrins, namely, aminolevulinic acid (ALA) and porphobilinogen (PBG), and often presented with a classical triad: abdominal pain, neurological dysfunction, and psychiatric disorders [7]. Around 80% of patients with acute or mixed porphyria are asymptomatic, but crises or acute attacks may be so severe as to require admission to intensive care units (ICUs) [9]. As there have not been any epidemiologic studies which investigate acute porphyrias in the ICU, difficulties in diagnosis, incidence, and prevalence of disease in the ICU remain uncertain. Four of nine types are classified as acute porphyrias, specifically aminolevulinic acid dehydratase deficiency porphyria, acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria [10].

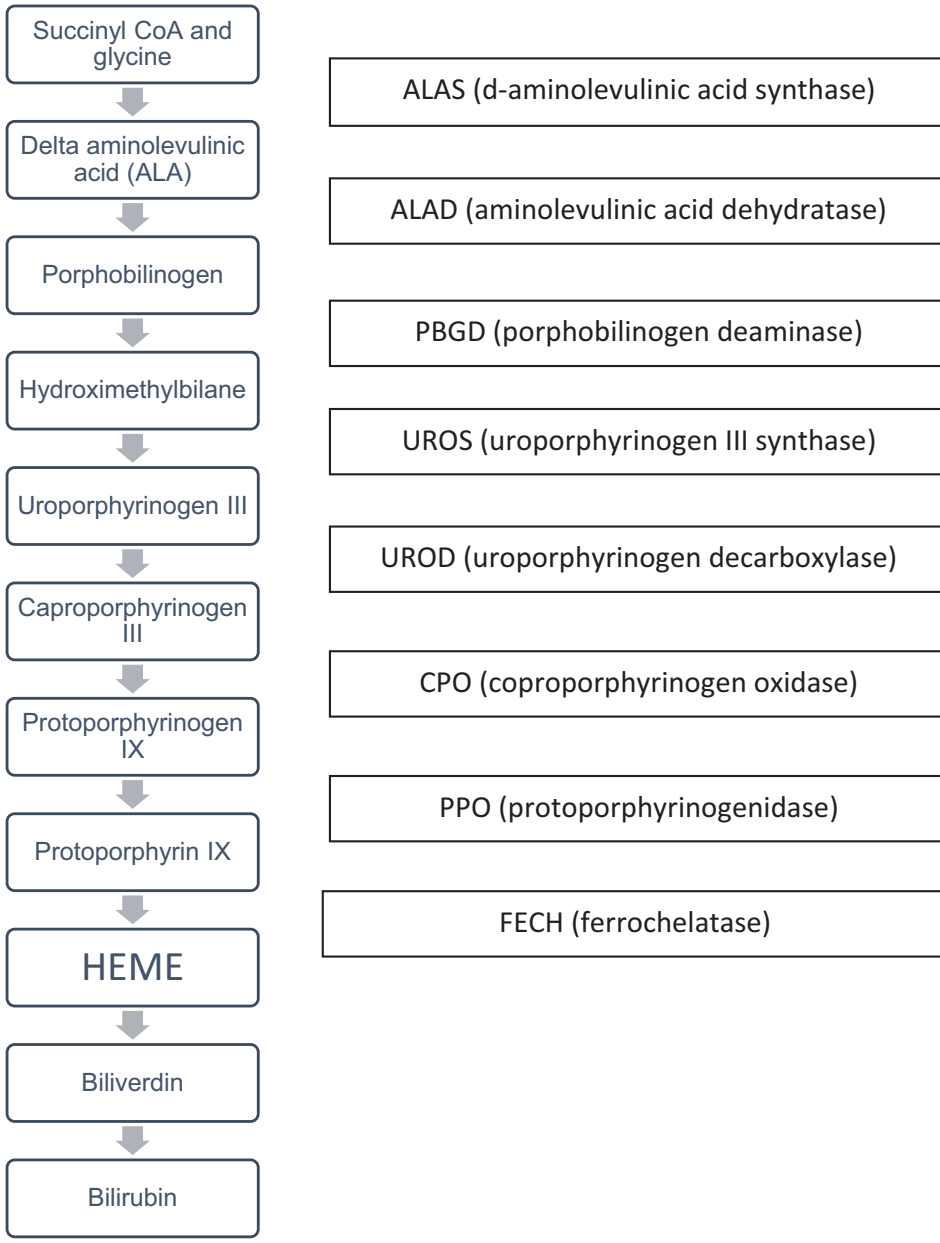

Fig. 53.1 The pathway of heme synthesis

Acute porphyrias are characteristically hepatic porphyria, and acute abdominal pain occurs in 90% of the patients. The pain is neuropathic and nausea, vomiting, and constipation may be additional symptoms. In acute porphyric crisis, neurological findings range from psychiatric disturbances to encephalopathy. Psychiatric disturbances include anxiety, paranoia, and hallucinations. Hypothalamic involvement and metabolic derangement of inappropriate secretions of antidiuretic hormone

Table 53.1 Drugs most commonly associated with the onset of crisis in acute porphyrias

Barbiturates	Carbamazepine	Ergotamines	Hydantoins	Griseofulvin
Methyldopa	Meprobamate	Pentazocine	Phenobarbital	Pyrazinamide
Primidone	Progestogens	Sulfonamides	Thiopental	Topiramate

lead to encephalopathy varying from confusion to psychosis. Seizures which may be triggered by hyponatremia or gastrointestinal loss from vomiting are reported in 30% of the patients. Myoclonic activity or coma may also be observed due to neurological effects or hyponatremia [11]. Neuropathy is another frequent condition in acute porphyria and reported in nearly half of the patients. Axonal neuropathy is more common than sensory neuropathy. Upper limbs are mostly involved, and motor weakness may be asymmetric and focal. Cranial nerves and respiratory muscles may be rarely involved, and progressive muscle weakness can lead to life threatening respiratory and bulbar paralysis. Autonomic dysfunction is a common condition. It may manifest as restlessness, tremors, urinary retention, paralytic ileus, tachycardia, and labile blood pressure. Labile blood pressure may cause difficulty in the treatment, and persistent hypotension, bradycardia, and sudden cardiac arrest are major causes of mortality [12]. Gastrointestinal sodium loss and syndrome of inappropriate antidiuretic hormone secretion from hypothalamic involvement are the main mechanisms of hyponatremia and may occur in 30% of the patients. As it may cause severe hyponatremia with serum sodium levels as low as 110 mg/dL, serum sodium levels should be monitored closely [8].

In genetically predisposed individuals, various precipitating drugs for acute porphyria are identified. The list of these drugs is depicted in Table 53.1.

53.3.3 Diagnosis

Diagnosis is mainly based on clinical suspicion. However, elevated aminolevulinic acid (ALA) and porphobilinogen (PBG) in urine are good screening tests. Although the rapid test, such as PBG in urine, which is easy to apply at the bedside is useful for patients with critical condition, they do not establish a definitive diagnosis, and it is necessary to determine enzyme hypoactivity and the concentration of porphyrin precursors in urine, plasma, and feces, and finally genetic studies are needed [13]. These tests should not cause a delay in initiating treatment. Guillain-Barré syndrome and heavy metal poisoning should be in the list of differential diagnosis.

53.3.4 Management and Therapy

The management of acute porphyrias attacks includes specific therapy and symptomatic treatment. Intravenous heme and carbohydrate loading are specific therapies. Intravenous heme is the most effective therapy and downregulates d-aminolevulinic acid synthase transcription. Thus, it leads to decrease in ALA and

PBG production. Intravenous heme should be performed 3–4 mg/kg/day for 4 days; if symptoms continue, additional courses may be required. Clinical improvement occurs in 1–3 days; therefore, in case of acute attacks, it should be used as soon as possible. When repeated treatment is performed, hepatic fibrosis and liver iron overload which are the main side effects of intravenous heme therapy should be considered. Glucose inhibits d-aminolevulinic acid synthase by affecting peroxisome proliferator activated receptor gamma coactivator-alpha. Therefore, carbohydrate loading was considered to be a standard treatment for acute attacks, but it does not alleviate symptoms as quickly as heme. When intravenous heme therapy is not available or in case of mild attacks, glucose can be used both orally and intravenously (300–500 g/day). After emergency intravenous glucose administration, oral nutrition with carbohydrates should be initiated as soon as possible [14, 15].

For symptomatic treatment of abdominal pain, acetaminophen and nonsteroidal anti-inflammatories are the first line therapy in mild attacks. However, parenteral narcotic analgesics usually require to control symptoms. Chlorpromazine can be used in managing nausea and vomiting. For sympathetic hyperactivity which leads to tachycardia and hypertension, beta blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers are preferred agents. Gabapentin, benzodiazepines, levetiracetam, or magnesium sulfate can be used to control seizures. Status epilepticus seizures require sedation with propofol. The management of hyponatremia and inappropriate secretions of antidiuretic hormone should be based on current guidelines [16].

53.4 Cyanide Poisoning

53.4.1 Introduction

Poisoning is an important healthcare problem resulting in hospitalization, utilization of healthcare resources, and high mortality. The 55 US poison control centers provided telephone guidance for 2.1 million human exposures, in 2020. The incidence of poison exposures is found as 6.4 for 1000 population and 18% of them were intentional. Ten percent of all poison exposures reported to the US poison control centers has major effect or caused death. Analgesics, sedatives, and antidepressants are the most common substances implicated in adult intentional poison exposures. Suicidal cyanide exposures are rarely reported: Intentional exposures accounted for 11 of the 205 cyanide poisoning cases reported to the American Association of Poison Control Centers in 2020 [17]. Cyanide exists in gaseous, liquid, and solid forms. Hydrogen cyanide (HCN or prussic acid) is a volatile liquid that boils at 25.6 °C. Industry widely uses nitriles as solvents and in the manufacturing of plastics. Nitriles may release HCN during burning or when metabolized after absorption by the skin or gastrointestinal tract. Also some synthesized and natural compounds produce HCN when burned. These combustion gases cause morbidity and mortality by smoke inhalation. Moreover, long-term consumption of cyanide-containing foods, such as cassava root or apricot seeds, may lead to cyanide poisoning [18].

53.4.2 Pathophysiology

Cyanide's main effect is the inhibition of oxidative phosphorylation by binding to the cytochrome C oxidase and blocking mitochondrial transport chain. Due to restriction in cellular respiration, cellular hypoxia and the depletion of ATP occur. Cellular metabolism shifts from aerobic to anaerobic resulting in hyperlactatemia and metabolic acidosis [19].

Intravenous application and inhalation of cyanide cause a more rapid onset of signs and symptoms than exposure via the oral or transdermal route by providing fast diffusion into the bloodstream. Acute cyanide poisoning rapidly affects the tissues with the highest oxygen requirements (such as the brain and heart). The concentration-time product capable of killing 50% of the exposed group (LCt50) for HCN is 2500–5000 mg/min/m^3. Vapor exposures in high concentrations (at or above the LCt_{50}) typically can cause death in 6–8 min. The lethal oral doses of HCN and cyanide salts are estimated to be 50 mg [20].

53.4.3 Presentation

The time period between exposure and the onset of symptoms depends on the route of entry and dose. The patient can present with symptoms as quickly as 1 min after inhalation and within a few minutes of cyanide ingestion. Onset of symptoms after exposure to nitriles may be significantly delayed. Because of being more sensitive to hypoxia, central nervous system and cardiovascular system dysfunction are most prominent. Nonspecific signs of cyanide poisoning are nausea, vomiting, headache, dizziness, and confusion. Due to cellular hypoxia, coma and seizures may occur. While in the early period of exposure tachypnea, tachycardia, and hypertension are the main symptoms, these findings can progress to apnea and bradycardia and cardiovascular collapse within 5–8 min of exposure [21]. The skin of patients may be slightly ashen in appearance despite tissue hypoxia due to elevated venous oxygen content resulting from failure of tissues to extract oxygen. Although cyanosis is not a prominent finding of cyanide poisoning, in case of prolonged hemodynamic failure and respiratory failure, cyanosis may occur. However, most of the patients have normal-appearing skin [22].

53.4.4 Diagnosis

Routine laboratory evaluation including blood glucose concentration, arterial and venous blood gas analysis, blood lactate level, and electrocardiogram should be performed. Cyanide toxicity is characterized by a normal arterial partial pressure of oxygen and a high venous partial pressure of oxygen resulting in narrowing of the venous-arterial PO2 gradient (<10%). High-anion-gap metabolic acidosis also is an important finding of cyanide toxicity [23]. Hyperlactatemia is a sensitive marker to diagnose cyanide toxicity. As carbon monoxide and hydrogen sulfide which are the

other inhibitors of oxidative phosphorylation may lead these findings to blood gas analysis, carboxyhemoglobin and methemoglobin levels should be obtained. Cyanide blood concentration could help to confirm the diagnosis, but the results are not available in time to be clinically useful and it may not correlate with toxicity [24]. Electrocardiogram abnormalities may include sinus bradycardia or tachycardia, supraventricular or ventricular arrhythmias, and atrioventricular blocks. Due to these nonspecific findings and absence of specific diagnostic test, clinicians should consider presentation and general clinical status of patients.

53.4.5 Management and Therapy

53.4.5.1 Supportive Care and Decontamination

Initial management of patients with acute cyanide poisoning requires rapid assessment and identification as cyanide can lead to death in a few minutes to a few hours. Airway, breathing, and circulation of patients should be stabilized, and intravenous access should be established. Following up patients in intensive care units provides effective cardiac and hemodynamic monitoring and advanced life support. Patients with suspected inhalation exposure should first undergo decontamination by being evacuated from the contaminated area and having affected clothing removed. For patients with the oral ingestion, emesis should not be induced. If administration is not contraindicated and patient is alert, a single dose of 50 g activated charcoal in patients with oral ingestion may be given [25].

53.4.5.2 Antidotes

After life support care and decontamination, antidotal therapy must be administered immediately. Especially if the patient has coexisting carbon monoxide poisoning, hydroxycobalamin is the first choice antidotal therapy. The standard dose is 5 g and it should be given intravenously over 15 min [26].

Cyanide antidote kit may be administered if hydroxycobalamin is not available. This kit contains amyl nitrite, sodium nitrite, and sodium thiosulfate. The nitrite components displace oxygen from hemoglobin to form methemoglobin, which attracts cyanide ions from the tissues to form cyanomethemoglobin. The sodium thiosulfate induces conversion of the cyanide to an excretable form of thiocyanate that is less toxic. Sodium nitrite and amyl nitrite in excessive doses induce dangerous methemoglobinemia and can cause death. Therefore, methemoglobin levels should be monitored and should not exceed 20%. Nitrites also may cause vasodilation and lead to hypotension. One ampoule of amyl nitrite should be crushed in a handkerchief and held in front of the patient's mouth for 15 s followed by a rest for 15 s. It may repeat 3–5 min until intravenous access established [25]. Amyl nitrite should be discontinued when sodium nitrite infusion is started intravenously. Sodium nitrite 10 mg/kg should be administered for 3–5 min. The dose for sodium thiosulfate is 12.5 grams and it should be given intravenously for 30 min [26].

Take-Home Messages

- Endocrine and metabolic disorders are serious conditions, and effective treatment should be initiated rapidly for better outcomes.
- Diabetic patients are usually admitted for the ICU in three different conditions: hyperglycemic crises, hypoglycemia, or metformin associated lactic acidosis.
- The patients with acute attacks of porphyrias usually require hospitalization, and many who presented with acute respiratory failure or central nervous system disorders need intensive care admission.
- Poisoning is an important healthcare problem resulting in hospitalization and high mortality. Although cyanide poisoning is rarely reported, it causes severe life threatening conditions due to the inhibition of oxidative phosphorylation.

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Diabetes Ketoacidosis: New Onset Diabetes with Diabetic Ketoacidosis After SARS-CoV-2 Infection in Adult Critically Ill Patient

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Contents

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Learning Objectives

- Diagnose diabetic ketoacidosis.
- Manage new onset diabetes in the ICU.
- Assess and manage complications of SARS-CoV-2 infection.

54.1 Introduction

The coronavirus disease 2019 (COVID-19) pandemic had an enormous impact on worldwide health, causing over 541 million confirmed cases and over 6.3 million deaths worldwide by June 26, 2022 (according to the WHO coronavirus disease situation report) resulting in high rates of hospitalization and intensive care unit (ICU) admission. Another long-standing global metabolic epidemic is diabetes mellitus (DM), which affected in 2021 about 537 million adults (463 million in 2019, + 16%), between 20 and 79 years of age (9.3% of world population in this age range). Several studies agree that diabetic patients infected with SARS-CoV-2 have a higher risk of hospitalization, pneumonia, and mortality. This is probably due to the chronic multiple metabolic and vascular abnormalities characterizing DM, leading to an inflammatory condition that can affect the response to pathogens. Furthermore, recent evidence highlighted a possible link between SARS-CoV-2 infection and occurrence of hyperglycemia or DM in previously nondiabetic subjects [1]. We thereby present the case of a 47-year-old woman, with no previous diagnosis of diabetes nor metabolic or familiar risks factors for DM, who was admitted to the ICU for coma and diabetic ketoacidosis associated to SARS-CoV-2 infection.

Case Presentation

A 47-year-old woman, not vaccinated against SARS-CoV-2, accessed the emergency room (ER) due to a state of coma. She was found at home in a drowsy state, with traces of blood in the oral cavity. Her family reported fever and malaise in the previous 2 days with simultaneous interruption of regular nutrition and hydration. In the last year, her family reported a state of anorexia nervosa with loss of about 60 kg in 6 months and regular consumption of herbal commercially available preparations, food supplements based on herbs, vitamins, and macro- and micronutrients. She was also under bisoprolol for unknown reasons. The remaining medical history was silent. At the ER, the patient appeared sleepy, opening her eyes spontaneously, emitting incomprehensible sounds, localizing painful stimuli and pushing it away, and not following simple orders and with no side deficits, defining a Glasgow Coma Scale (GCS) of 11 (E4, V2, M5). Arterial blood gas (ABG) analysis was performed, showing severe metabolic acidosis (pH 6.7, $paCO_2$ 16 mmHg, HCO_3^- 5 mmol/L, BE −33 mmol/L) and severe hyperglycemia (530 mg/dL). Nasopharyngeal swab for SARS-CoV-2, routinely executed due to the pandemic, was positive, and chest X-ray reported a left-side basal pulmonary thickening. Nevertheless, oxygenation was not impaired (P/F 488 mmHg), and respiratory rate (RR) was normal (20 acts/min), with no respiratory distress. She was initially administered crystalloids (500 mL NaCl 0.9%, intravenous (IV)) and 100 mEq HCO_3-IV, with small improvement of pH

to 6.9. In consideration of the SARS-CoV-2 positivity, severe neurological impairment, and metabolic imbalance with difficult-to-control hyperglycemia, she was admitted to the COVID-19 intensive care unit.

54.2 Investigations

At ICU entrance, we performed a complete clinical examination, electrocardiogram (ECG), ABG, urine strip test, and laboratory tests, according to the current guidelines (Italian Society of Diabetes, SID).

On clinical examination, ER's neurological presentation was confirmed. The patient had become tachypneic (25/30 acts/min) and hypocapnic ($PaCO_2$ 26 mmHg), with good peripheral oxygenation (96%). Hemodynamically, she was tachycardic (120/bpm), with a 100/50 mmHg blood pressure. ECG confirmed tachycardia. Heart ultrasound showed a good ventricular contractility, a right ventricle kissing, and a small and collapsible inferior cava vein. The patient referred no abdominal pain. ABG test showed a partial correction of the severe metabolic acidosis: pH 7.23, pCO_2 26 mmHg, pO_2 62.6 mmHg, SpO_2 95%, HCO_3^- 13.6 mmol/L, BE −16.4 mmol/L, lactate 1.1 mmol/L, and P/F 298 mmHg. The anion gap was 26.5 mmol/L. Abdominal CT scan was also conducted showing bilateral basal pulmonary consolidation and no abdominal organ alteration.

We performed a urine strip test, consisting of a plastic or paper tape with pads impregnated with chemicals reacting with compounds in the urine to produce a characteristic color. The analysis can diagnose the presence of protein, glucose, ketones, hemoglobin, bilirubin, urobilinogen, acetone, nitrite, and leukocytes, in addition to tests for pH or tests for infection by various pathogens. Some strips only give qualitative information, while other semiquantitative data even provide an estimate of a quantitative result. The results are read by comparing the colors of the pads with a chromatic scale provided by the manufacturer, and semiquantitative values are generally reported from trace to 4+. Our urine strip test resulted positive for glycosuria and ketone bodies (4+ and 4+) and the patient was in polyuria, while laboratory tests showed leukocytosis (WBC 19,120 × 10^3/μL, with 15,400 × 10^3/μL neutrophils), Hb 15.9 g/dL, HT 51%, PLT 262,000/μL, creatinine 1.16 mg/dL, Na^+ 147 mmol/L, K^+ 3 mmol/L, Cl^- 108 mmol/L, and normal pancreatic enzymes (serum pancreatic isoamylase 10 U/L, pancreatic lipase 8 U/L). Signs of inflammation (high C-reactive protein, globular sedimentation rate, IL-1, IL-6, and ferritin), hypercoagulability (D-dimer 8.29 mg/L, INR 1.34, APTT 2.57), high glycated Hb (157 mmol/mol. Range 23–43), and serum cortisol (2072 mg/day. Range 58–403) were also reported.

Box 54.1 ICU Investigations on Admission

1. Complete clinical examination
2. ECG
3. Blood gas analysis
4. Urine test strip
5. Laboratory tests

54.3 Differential Diagnosis

Many different causes can determine coma. However, patient's ABG test led us to associate coma with severe metabolic acidosis, while high anion gap and severe hyperglycemia guided us to diagnose diabetic ketoacidosis (DKA). Before focusing on our primary diagnosis, we excluded the following conditions. Alcoholic ketoacidosis should have been considered if history of ethylism, high alcoholemia, and ketonuria were documented, but glycemia should have been only slightly increased (due to glycogenolysis and neoglycogenesis promoted by counter-regulating hormones in response to fasting) or even lower than normal. We excluded lactic acidosis due to normal lactate on ABG analysis: In lactic acidosis, lactates are higher than 1.3 mmol/L, ketosis is absent, and hyperglycemia is modest. Finally, we excluded proximal renal tubular acidosis, where blood sugar is normal, ketonuria is not present, the urinary pH is>5.5, and the anion gap is normal. Other conditions that we took into account on differential diagnosis of coma were hepatic encephalopathy, uremia, intoxication, stroke, intracranial expansive processes, meningoencephalitis, dystonia, carbonarcosis, and syndrome of inappropriate ADH secretion (SIADH).

Box 54.2
Biochemical Criteria for DKA Diagnosis [2]

Hyperglycemia (blood glucose >200 mg/dL (or 11 mmol/L); Venous pH <7.3 or serum bicarbonate <15 mmol/L (Venous pH is 0.02–0.15 units below arterial pH while venous bicarbonate levels are 1.88 mmol/L higher than arterial levels); and ketonemia or ketonuria. DKA severity is categorized by the degree of acidosis: mild (venous pH <7.3 or serum bicarbonate <15 mmol/L), moderate (pH <7.2 or serum bicarbonate <10 mmol/L), or severe (pH 7.1 or serum bicarbonate <5 mmol/L).

54.4 Treatment

As our patient fulfilled the criteria for severe DKA, our target was to normalize blood glucose level, correct dehydration and acidosis, and reverse ketosis. Rehydration and normalization of glycemia were the first mandatory steps to reverse metabolic acidosis coma. We initially administered crystalloids to promptly normalize blood volume, reduce osmolarity and glucose levels, and increase renal perfusion and urinary clearance of glucose and ketone bodies. We also started the infusion of IV insulin, targeting maximum serum ketone body reduction by 0.5 mmol/L/h, circulating bicarbonates increase by 3 mmol/L/h and capillary blood glucose reduction by 3 mmol/L/h, to avoid cerebral edema. After the resolution of the acute phase, we administered balanced fluid solutions, to maintain a slightly positive fluid balance, and continuous infusion of insulin, using an IV infusion pump (concentration 50 UI/50 mL NaCl 0.9%) and maintaining blood glucose between 150 and 200 mg/dL

using an internal algorithm based in the regular assessment of glycemia (every 2 h). Arterial blood pressure, central venous saturation, urine output, central venous pressure, and heart and vena cava ultrasound were daily monitored to assess fluid responsiveness and tolerance and to avoid overload.

Our patient had potassium and phosphate deficiency, as well as tendency to hypernatremia, as what typically happens in DKA, due to urinary or gastrointestinal losses, rehydration, and insulin treatment. We gradually replaced potassium at a maximum rate of 20 mEq/h; treated global phosphate deficiency adding 20–30 mEq of phosphate to each liter of solution infused for the first days, monitoring calcium levels to avoid tetany; and daily calculated the serum sodium levels that we expected under the effect of administering insulin alone, to correct concentration. We didn't administer HCO_3^-, since most patients reach metabolic equilibrium with rehydration and insulin, especially if their arterial pH is >7.0.

Box 54.3
- Rehydration and glucose level normalization
- Potassium supplementation
- Bicarbonate administration
- Supply phosphate deficiency
- Sodium balance

54.5 Evolution, Outcome, and Follow-up

During the first days after ICU hospitalization, correct blood volume replenishment, adaptation of glycemia, and nutrition permitted us to control the metabolic aspect allowing weaning from continuous IV infusion of insulin after 12 days. Meanwhile, suspecting a pulmonary septic overlap, hydrocortisone (4.25 mg/kg/day) and ceftriaxone (2 g/day) were started, and hemodynamics was progressively supported by noradrenaline to maintain a MAP >70 mmHg (maximum dosage 0.5 μg/kg/min). During the first night, due to persistent impairment of neurological state and worsening of gas exchanges, we proceeded with orotracheal intubation and mechanical ventilation (MV) to support the patient. During MV, we adjusted sedation with morphine (mean dosage 0.42 mg/kg/day) and propofol (mean dosage 2.5 mg/kg/h). Several multiresistant microorganisms responsible for a superinfection were later isolated: Respiratory tract cultures revealed an infection due to *Stenotrophomonas maltophilia* (on 5th day after admission) and *Aspergillus flavus* (on 7th day), while blood cultures revealed a multiresistant *Staphylococcus epidermidis* infection on 15th day. The adaptation of antimicrobial therapy granted progressive improvement of inflammatory indexes and amine's decalage until suspension after 2 weeks. Patient's respiratory failure, probably SARS-CoV-2 and *Stenotrophomonas maltophilia* related, worsened during the first week in ICU, requiring two cycles of prone positioning, with benefit. Patient later developed pneumothorax first on the left and then on the right lung, complicating weaning from MV. However, progressive reduction of MV

and sedation allowed extubation on the 22nd day. After that, an evident picture of global asthenia (compatible with a picture of critical illness polyneuropathy) required the execution of tracheostomy on the 25th day, useful to maintain the target to wean from MV.

The patient was finally discharged on the 34th day: She was vigilant and collaborative but affected by depression; eupneic, spontaneously breathing through tracheostomy, with no thoracic drainages in situ; apyretic with stably negative inflammatory indexes after suspension of antimicrobial therapy; still affected by global asthenia but collaborative to daily physiotherapy; and on therapy with subcutaneous long-acting and regular insulin, with normal hemodynamics and diuresis.

She was firstly admitted to the Pneumology Unit for 31 days and secondly admitted to the Rehabilitation Department for 3 months. Her evolution was characterized by persistent need of insulin therapy (long-acting insulin 12 IU/day, plus regular insulin 5 IU before meal when glycemia is >150 mg/dL), both difficult enteral (due to abdominal pain and feeling of gastric fullness) and oral (due to dysphagia) feeding onset, persistent depressive mental state, and diffuse pain, with progressive physical rehabilitation.

On discharge, insulin therapy was still necessary. The patient had the tracheostomy removed, has fully recovered oral feeding capacity, and was able to walk for short-medium distances with a four-wheel walker.

54.6 Discussion

We presented the case of a 47-year-old woman with no personal or family history of diabetes nor metabolic or familiar risk factors for DM, diagnosed with DKA related coma secondary to SARS-CoV-2 infection. The patient presented neurological impairment, critical metabolic acidosis, hyperglycemia, and ketonuria on admission, meeting biochemical criteria for severe DKA. Rehydration and normalization of glycemia and serum electrolytes resolved the acute phase, while chronic administration of insulin permitted to maintain normal blood glucose levels on admission and after discharge.

Insulin-dependent DM accounts for approximately 5–10% of diabetes in adults, the occurrence peak is typically in the fifth decade, and DKA may be the initial presentation in almost 25% of adults with newly diagnosed type 1 diabetes (T1DM) [3]. Family history is a well-known risk factor for T1DM, while little evidence is available on environmental risk factors. Our patient presented few relevant aspects regarding her previous clinical history: While severe caloric restriction has only been associated with type 2 diabetes (with controversial evidence on his protective or harmful effect [4]), viral illnesses are more likely to play some role in T1DM.

Many research groups highlighted the association between diabetes and a higher risk to develop severe COVID-19, requiring hospitalization and intensive care [5]. Whether higher risk of critical SARS-CoV-2 infection in diabetic patients is known, some evidence suggests a bidirectional relationship between diabetes and COVID-19. SARS-CoV-2 expresses in its envelope a protein called protein S that binds with high affinity to the extracellular domain of ACE2 enzyme, expressed in alveolar epithelial cells, causing membrane damage and lung fibrosis. It has recently been shown that

the expression of ACE2 in the pancreas (mainly in islet cells) is even higher than in the lungs. Therefore, SARS-CoV-2 may be able to bind this receptor and enter pancreatic β-cells, provoking cellular dysfunction and hyperglycemia. Interestingly, only 1–2% of patients with mild COVID-19 infection have pancreatic lesions, while 17% of patients with severe cases have pancreatic damage [1]. Several data seem to support this hypothesis in childhood, reporting increased percentage of new childhood T1DM during pandemic in concomitance with SARS-CoV-2 infection [6], while poor evidence is available regarding this phenomenon in adult patients, as reported instead in this clinical case.

Although hyperglycemia increases COVID-19-related mortality and morbidity, we can finally suppose that the virus itself can induce/worsen hyperglycemia, culminating in a vicious cycle, both in child and in adult patients. While now we understand the intriguing bidirectional mechanism between SARS-CoV-2 and diabetes, still unanswered remain questions regarding long-term duration of COVID-19-induced pancreatic β-cell damage and weather SARS-CoV-2 could persist in β-cells, causing chronic infections.

Take-Home Messages

- The association between coma and SARS-CoV-2 positivity should suggest further investigations looking for glycemic decompensation.
- Diabetes ketoacidosis could be the primary symptom of underlying COVID-19.
- Still remain unclear the temporary or chronic long-term effects of SARS-CoV-2 associated diabetes mellitus.

1. Which are the biochemical criteria for DKA diagnosis?
2. How can you differentiate between diabetic ketoacidosis and different conditions causing coma?
3. Explain the mechanism underlying SARS-CoV-2 induced pancreatic β-cell damage?

Summary

Diabetes is one of the most frequent comorbidities in people affected by COVID-19 with a prevalence ranging between 7 and 30%. SARS-CoV-2 infected diabetic patients have a higher rate of hospital admissions, severe pneumonia, and higher mortality than nondiabetic individuals. Chronic hyperglycemia can impair innate and humoral immunity, and diabetes is associated with a chronic metabolic and vascular inflammatory state that favors the onset of acute respiratory distress syndrome and superinfections. Recent evidence has shown that even SARS-CoV-2 virus is capable of causing direct damage to pancreatic β-cells that could trigger hyperglycemia and even induce the onset of diabetes in previously nondiabetic individuals. This evidence has been confirmed in childhood, while few data regarding adult patients are available. We reported a clinical case regarding a 47-year-old woman admitted to the intensive care unit for coma due to diabetic ketoacidosis secondary to SARS-CoV-2 infection. The patient was successfully treated with acute rehydration, normalization of glycemia, and chronic administration of insulin to maintain normal blood glucose levels.

Control of blood glucose on admission in SARS-CoV-2 patients admitted due to a state of coma is suggested to reduce the incidence of complications and decrease the burden on health systems.

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Acute Intermittent Porphyria: A Challenging Diagnosis and Treatment

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Contents

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Learning Objectives

- To understand that acute intermittent porphyria is a complex disease that causes crises that are very difficult to diagnose due to the heterogeneity of the symptoms and psychiatric disorders
- To identify the guiding signs and symptoms that allow us to focus our diagnostic hypotheses in acute intermittent porphyria
- To holistically evaluate patient's clinic and past medical history to reach a conclusion that allows us to integrate all the elements under the diagnoses of acute intermittent porphyria
- To understand the importance of early medical treatment in the case of porphyria crises, given that a delay in directed treatment can endanger patient's life and lead to important sequelae in the medium and long term

55.1 Introduction

Among all types of diseases and ailments, some of the most frightening for resident doctors are those that can evolve rapidly and surreptitiously from banal pathologies to serious and potentially lethal conditions. This is the case for diseases with a metabolic profile, including acute intermittent porphyria.

Acute intermittent porphyria is an acute neurovisceral porphyria due to a partial deficit in the synthesis of the heme-group by the enzyme porphobilinogen deaminase (PBGD). It is caused by a genetic disorder that is usually transmitted by autosomal dominant inheritance but with low penetrance [1]. The presence of the same genetic alteration can give rise to different phenotypes, and its pathogenic expression has been linked to environmental factors, which in many cases act as a trigger for the characteristic crises of this disease [2].

The clinical presentation is very diverse, and the symptoms are often nonspecific. Thus, the first diagnostic tool we need is clinical suspicion, since confirmatory tests and especially those for characterizing the type of porphyria are slow and not always available depending on our workplace. Among other symptoms, crises may present with abdominal pain, dysautonomia, hydroelectrolytic disorders, seizures, and neuropathy which, if it affects the respiratory system, may pose an emerging life threat to these patients [3].

Case Study

Case Presentation

A 30-year-old woman presented to the Emergency Department for abdominal pain. She was a regular smoker of tobacco and cannabis, with sporadic consumption of alcohol and cocaine. She had a history of a borderline mucinous tumor/proliferative atypical mucinous tumor in the left ovary (FIGO IA) surgically treated 2 years prior and followed up in gynecology consultations, with control CT scans without distant disease. She also had a history of anxious-depressive syndrome with irregular follow-up, together with episodes of kleptomania in childhood. She received home treatment with escitalopram 10 mg

every 24 h, mirtazapine 15 mg every 24 h, and alprazolam 1 mg on demand. In addition, the patient had several visits over the years to her family doctor with abdominal pain, mostly interpreted as gastritis related to dietary transgressions, viral gastroenteritis, dysmenorrhea, etc. These had not been reviewed as a whole, as the episodes occurred several months apart.

The patient presented to the Emergency Department with severe diffuse abdominal pain of 4 days' duration, associated with nausea and vomiting. The patient had no other symptoms. At the onset of the symptoms, the patient went to her family doctor who prescribed first-line analgesic with little improvement. So, the patient returned several times and, finally, she was referred to the Emergency Department. On that first visit to the Emergency Department, the patient asked for voluntary discharge without waiting for the results of the blood and urine tests that had been requested. The following day the patient returned to the Emergency Department with the same symptoms. When the complementary tests from the previous day were reviewed (slight leukocytosis with slight neutrophilia in the blood and leukocyturia with positive nitrites in the urine), she was diagnosed with a urinary tract infection and prescribed outpatient analgesic and antibiotic treatment with paracetamol 1 g orally every 8 h and fosfomycin 3 g orally in two doses on consecutive days.

Despite the initial treatment, the pain persisted, so the patient went back to the Emergency Department 36 hours later. This time an assessment by the internal medicine physician on-call was requested. Hospital admission was decided to optimize pain control under diagnostic suspicion of urinary tract infection and vomiting probably related to increase in cannabis use.

55.2 Investigations

The initial physical examination revealed nothing more than an asthenic habitus. The patient had normal vital signs and normal neurologic, cardiopulmonary, and abdominal examination. Once on the hospital ward, the physical examination was repeated, revealing high blood pressure (180/117 mmHg). In addition, the patient complained of appearance of numbness in both legs. A battery of basic diagnostic tests was carried out. The blood test revealed a hyponatremia of 130 mmol/L. The urine culture was negative. Besides, a Hoesch test was performed with a positive result, but, as the patient was menstruating, it was interpreted as a contamination, leaving the test of no value. This Hoesch test was performed according to Lamon J. modification of 1974, which consists of a preparation of 2–3 mL of Ehrlich's "modified" reagent (20 g p-dimethyl-aminobenzaldehyde diluted to 1000 mL with HCl, 6 mol/L) with two drops of fresh patient's urine added on top of that. This test is considered positive when the solution changes instantaneously to a cherry-red color, present initially at the top of the solution but throughout the tube on brief agitation.

Considering the almost normal blood test results and the absence of data on the organic origin of the pain, and given the patient's history of mental health disorders, a psychiatric assessment was carried out. Although it seemed unlikely to be a somatoform disorder, the psychiatrist noted anxious symptoms in a patient with Cluster B personality traits.

In addition, given the persistence of abdominal pain with constipation and complaints of sensory alterations in the extremities, an electroneuromyogram, a chest X-ray, and an abdominal ultrasound were performed, all with normal results. At that point, the patient was evaluated by a gynecologist who found no pathological findings. Furthermore, she was also evaluated by a dermatologist, as she had developed erythematous scaly lesions on both elbows, which they were interpreted as irritative eczema.

Throughout her admission, the patient repeatedly broke the hospital rules, leaving the hospital for hours with her partner or family members despite warnings from the medical team. She also had problems of insomnia and poor emotional control, frequently arguing with her room companions, switching from laughing to crying during the same conversation on several occasions, and even presenting a psychogenic syncope witnessed by the nursing staff.

On a physical level, the patient presented slight improvement in abdominal symptoms but with the appearance of pain in both arms and legs along with a sensation of lack of strength that could not be detected in the physical examination. Thus, she was assessed by a neurologist and a cervical MRI was performed with normal results, finding no organic cause for her symptoms.

Some analytical parameters had to be sent to external reference laboratories. Lead blood levels and the activity of PBGD were reported as normal (result of 120 pmol/mg protein in 30 min with the limit of normality being >66 pmol/mg protein in 30 min). The latter test has a sensitivity of 95% for the diagnosis of acute intermittent porphyria, so this diagnosis was initially ruled out pending the results of blood porphyrins (which were still pending).

After 10 days of admission, the only nonsubjective data of pathology were the blood pressure figures, which remained high despite two antihypertensive drugs. For this reason, hospital admission was extended pending studies to rule out secondary hypertension. Serum and urinary catecholamine levels were measured. Excess noradrenaline and to a lesser extent adrenaline were found (dopamine, cortisol, and aldosterone were normal). A Doppler ultrasound of renal arteries showed no evidence of renal artery stenosis.

The patient presented progressively increasing pain, altered sensation, and lack of strength in all four limbs. However, during the daily physical examination, it was not clear whether this was a voluntary condition, with normal osteotendinous and plantar cutaneous reflexes.

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After 18 days of hospitalization, a new Hoesch test was carried out due to the persistence of the patient's symptoms. The result was again positive, so it was decided to collect 24-h urine to determine urinary porphyrins. However, before the study could be completed, the patient presented an abrupt episode of dyspnea and inability to mobilize respiratory secretions. Arterial blood gases analysis showed a severe acute respiratory failure (pO2 50.5 mmHg, pCO_2 42.3 mmHg) despite high-flow oxygen therapy. The on-call intensivist was contacted, and the patient was admitted to the intensive care unit (ICU) 19 days after her admission.

Upon admission to the ICU, noninvasive mechanical ventilation was initiated. The patient remained hemodynamically stable with good ventilatory mechanics.

55.3 Differential Diagnosis

Upon admission to the ICU, in addition to abdominal pain, the patient presented pain and weakness in the proximal region of the limbs, to the point that she was unable to adequately mobilize respiratory secretions and required ventilatory support.

A differential diagnosis with other entities, mainly neurological, could be considered if we are guided by weakness as the main symptom. Thus, we should assess conditions such as a myasthenic crisis (especially given the patient's age and sex), Guillain-Barré syndrome, or lead poisoning [4]. However, if we consider other signs and symptoms that are described in her medical history, the suspicion of porphyria increases: psychiatric alterations, insomnia, abdominal pain with poor response to analgesia, constipation, hypertension, elevated catecholamines, hyponatremia, and a positive Hoesch test in two occasions.

All this led us to the diagnostic hypothesis of an acute porphyria crisis. Treatment should therefore be started, even without knowing which type of porphyria we were dealing with. In order to reach a more precise diagnosis, 24-h urine was collected for determination of porphyrin fractions, and a malar lesion that appeared during hospitalization was biopsied.

55.4 Treatment

In view of the severity of this condition, it was decided to start treatment with carbohydrate overload (400 g of glucose per day) together with intravenous hemin (150 mg per day, approximately 3 mg/kg of weight per day).

On the same day he was admitted to the ICU, oxygen therapy requirements were reduced to FiO_2 0.4 while the patient remained hemodynamically stable, with an adequate level of consciousness and without any other organic dysfunction.

The patient's evolution in the ICU was favorable, with some occasional episodes of desaturation which were interpreted as atelectasis and which were resolved with postural changes. The patient was maintained on intravenous hemin for 96 h, as well as carbohydrate-enriched nutrition. The patient was weaned from noninvasive ventilation to conventional oxygen therapy, and oral nutrition was started, with good response. The patient was discharged back to the hospital ward 6 days after admission to the ICU.

55.5 Evolution, Outcome, and Follow-up

Once on the hospital ward, the pending analytical results were received. A clear elevation of porphobilinogen and uroporphyrins in the urine and less clear elevation of urinary coproporphyrins and porphyrins in the feces were detected. All these data led to the diagnosis of acute intermittent porphyria. Thus, a genetic study was requested to confirm the diagnosis.

During her second period on the ward, the patient presented new episodes of stabbing pain in the limbs. She required the administration of new cycles of hemin and an increase in the dose of analgesic medication (strong opioids, neuromodulators, and conventional analgesia) for pain control. The patient was very limited in terms of mobility. The electroneuromyogram was repeated and showed data of pure motor axonal polyneuropathy of proximal predominance with data of active denervation. This situation required multiple rehabilitation sessions to be able to walk again.

During the following weeks on the ward, the patient developed bacteremia related to a peripherally inserted central catheter due to *Staphylococcus epidermidis* and a urinary tract infection due to *Enterococcus faecalis*, both requiring antibiotic treatment. Both infectious complications were associated with new porphyria crises, and these crises were confirmed by significant elevations in urinary porphyrin levels.

Genetic analysis showed the presence in heterozygosis of a pathogenic variant of the HBMS gene in position +1 of intron 2 (c.87+1G>A). This variant had already been described in a family affected by acute intermittent porphyria, thus confirming our patient's diagnosis.

Considering the need for multiple cycles of intravenous hemin and the poor symptomatic control despite analgesia and a carbohydrate-rich diet, an authorization from the Ministry of Health was requested to start this patient on a recently approved drug (givosiran) for chronic treatment of this disease. Givosiran is a δ-aminolaevulinic acid synthase 1 (ALAS1)-directed small interfering RNA (siRNA) approved for the treatment of acute hepatic porphyria [5, 6]. Given that the authorization could be delayed for a long time and in view of the patient's good clinical evolution, it was decided to discharge her 16 weeks after her admission to hospital. At discharge, the patient was able to walk with assistance and raise both arms above her head, but she still required high doses of analgesia and assistance with many of the basic activities of daily living.

55.6 Discussion

This case of acute intermittent porphyria highlights that patient's symptoms and medical history are essential to reach a diagnosis. During the first weeks of admission, several diagnostic tests were performed with normal results, while the neuropathic symptoms progressively worsened. Probably, the diagnosis could have been reached earlier if the causes of neuropathy without early involvement of the electroneuromyogram had been sought.

Another important aspect to bear in mind is that when a gradually increasing health problem is detected, it must be carefully assessed to anticipate a possible worsening that could put our patient's life at risk. When our patient complained of great difficulty in walking, the electroneuromyogram was not repeated, and she finally required urgent admission to the ICU due to respiratory muscle impairment. Moreover, when we see patients with conditions that we are not able to identify at first, it is useful to stop, think, and reevaluate all the data we have. In our case, this served to bring together signs and symptoms as different as hyponatremia, hypertension, psychiatric alterations, abdominal pain, and neuropathy into a single clinical entity, the acute intermittent porphyria.

In certain metabolic diseases, early diagnosis and treatment are essential to avoid or minimize the sequelae. In our case, despite having administered a correct treatment on admission to the ICU, the patient presented significant mobility limitations later, requiring assistance for normal activities of daily living almost 4 months after her admission to hospital. It is also important to underline how in our case an intronic alteration has been responsible for a life-threatening disease. In fact, the drug for which approval was sought acts on this lesser known pathway of storage of genetic material, formerly called "junk DNA."

Finally, when caring for complex patients with such diverse symptoms, it is important to manage certainty. A normal result of the PBGD activity rules out up to 95% of acute intermittent porphyria. This normal result should be integrated on a case-by-case basis. We must consider that even with such a low diagnostic possibility, it may still be one of the most important diagnostic hypotheses to rule out in order to avoid the damage that a diagnostic delay may cause.

Take-Home Messages

- Acute intermittent porphyria is a clinical entity that poses a diagnostic challenge given the heterogeneity of its symptoms. A holistic view of the patient is key to its accurate and early identification.
- Early targeted treatment for acute porphyria crises, even if we have not yet identified the acute porphyria subtype, is essential to reduce the risk of developing sequelae and to minimize the occurrence of severe and potentially life-threatening symptoms.
- A negative result of a high-sensitivity complementary test (PBGD activity) should not be enough to completely rule out the diagnostic possibility of acute intermittent porphyria, especially if there are other tests that allow its identification and when such an entity may put the life and quality of life of our patient at risk.

Summary

A 30-year-old woman presented to the Emergency Department for abdominal pain. During her admission, psychiatric alterations, hyponatremia, and arterial hypertension were observed. Multiple tests were carried out with negative results, including a determination of an enzyme which is decreased in 95% of the cases of acute intermittent porphyria. The patient progressively developed neuropathy that ends up causing respiratory failure that required admission to the ICU for ventilatory support. She was then diagnosed with an acute porphyria crisis (based on her symptoms and a positive Hoesch test). Targeted treatment with carbohydrate overload and IV hemin was established. Subsequently, the specific diagnosis of acute intermittent porphyria was reached by genetic analysis and urine, fecal, and serum porphyrin fraction analysis. After ICU discharge, the patient presented new crises that did not require readmission to ICU, though she required new cycles of IV hemin. This situation motivated the request for approval of a modern drug (givosiran) as maintenance treatment. Finally, the patient was discharged from hospital with significant mobility sequelae, requiring daily rehabilitation sessions and help to carry out basic activities as walking. This case shows how a holistic view of the patient's problems guided by the clinical signs can be the key for reaching a difficult diagnosis and starting a targeted treatment as soon as possible.

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Mitochondrial toxicity and arterialization of venous blood

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Contents

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Learning Objectives

- Describe the physiology of oxygen supply and consumption in humans.
- Interpret and explain the possible mechanisms of mitochondrial toxicity.
- Discuss cyanide toxicity and poisoning pathophysiology, diagnostics, and therapeutic approach.

56.1 Introduction

Mitochondrial toxicity causes dysoxia, or abnormal tissue oxygen utilization. To maintain energy production, cells are forced to switch to the less efficient anaerobic metabolism that ultimately leads to cell death, multi-organ dysfunction, and death. Cyanide is one of the most common mitochondrial toxicants.

Although this is a rare cause of admission to the intensive care unit, it should be considered in the differential diagnosis of a patient presenting with severe shock and multi-organ dysfunction and hyperlactacidemic metabolic acidosis, without other more frequent possible etiologies such as sepsis or regional ischemia.

Case Presentation

A 63-year-old male was brought into our intensive care unit (ICU) from a subacute care hospital for loss of consciousness. He was there recovering from an aortic aneurysm surgery in which a Dacron graft was inserted 3 weeks earlier, without any relevant complications. He had a medical history of arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, GOLD B, and major depression syndrome.

He was found unconscious 3 h prior and had left a goodbye note in his room. He showed a Glasgow Coma Scale (GCS) score of seven points (ocular 1, verbal 1, motor 5), without any improvement after administering a total amount of 1.2 mg of naloxone and 1 mg of flumazenil suspecting opoid or benzodiazepine intoxication. He also presented with hypotension (systolic blood pressure/diastolic blood pressure, 66/35 mmHg). He was intubated without any complications and transferred to our center. He presented neither fever nor other infectious symptoms in the previous days.

Upon arrival at our unit, he was analgosedated, under mechanical ventilation, with a mean blood pressure above 65 mmHg on a 0.23 mcg/kg/min noradrenaline infusion and showing clear signs of tissue malperfusion.

56.2 Investigations

Intentional self-inflicted intoxication was suspected when the farewell note was found. Therefore, a comprehensive screening for toxics in both blood and urine was requested.

Arterial and central venous catheters were placed for drug administration and hemodynamic monitoring. Strangely, blood samples taken from the central venous

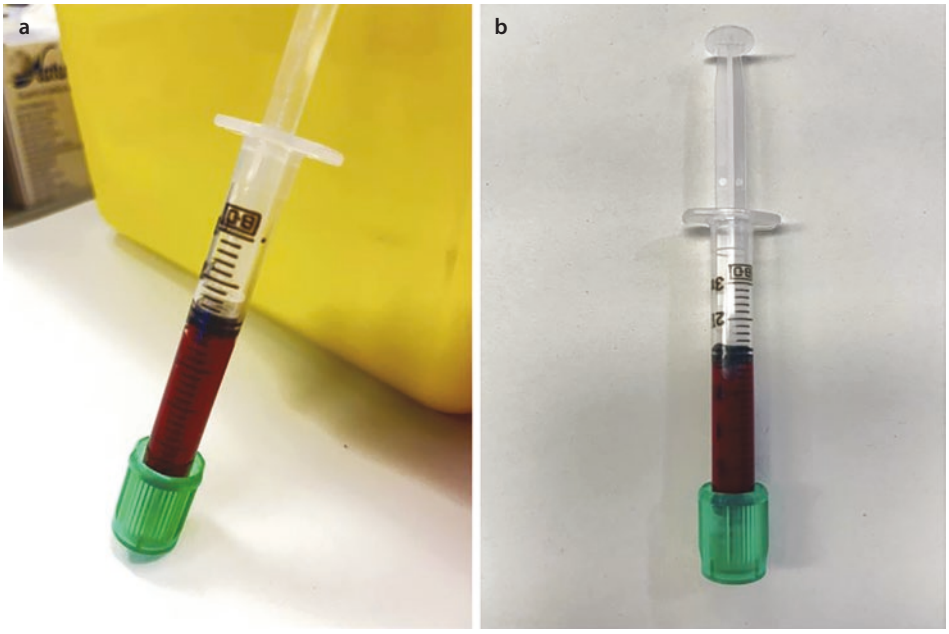

Fig. 56.1 Visual appearance of the first samples obtained from the left femoral artery catheter (**a**) and the distal lumen of the right femoral central venous catheter (**b**). Note the similarity in color of both blood samples

catheter were bright red, showing arterial characteristics (Fig. 56.1). Correct placement of the catheter at the entrance of the right atrium was confirmed both by ultrasound and chest X-ray.

Point-of-care blood analysis both from arterial and central venous blood samples showed a severe metabolic acidosis (pH 7.05, HCO3 12.5 mmol/L) with high anion gap (27.7 mmol/L) and hyperlactatemia (17.4 mmol/L).

Furthermore, central venous oxygen saturation (SvO_2) was 94.7% with central venous oxygen partial pressure (PvO_2) 72 mmHg, being the arterial oxygen saturation (SaO_2) 99.7% and arterial oxygen partial pressure (PaO_2) 118 mmHg, respectively. Therefore, the oxygen blood content was 16.5 mL/dL in arterial blood (CaO_2) and 15.5 mL/dL in central venous blood (CvO_2), with an oxygen extraction rate of 6.1% (normal value 20–30%). Arterial to venous CO_2 gap was in normal values (5 mnHg) showing that tissue blood flow was adequate.

Advanced hemodynamic monitoring by pulse wave analysis calibrated by transpulmonary thermodilution (PiCCO® system) was initiated, obtaining values compatible with distributive shock (Fig. 56.2). Bedside echocardiography showed normal biventricular systolic and diastolic function with no significant segmental or valvular heart disease and no signs of pulmonary arterial hypertension or pericardial effusion.

Taking into account hemodynamic data, the oxygen delivery index (DO_2i) was adequate at 561 mL/min/m^2 (normal range 500–650), but the oxygen consumption index (VO_2i) was extremely low at 34 mL/min/m^2 (normal range 115–185).

Variable	Value	Normal range
Cardiac output (L/min)	7.1	4.0-8.0
Cardiac index (L/min/m2)	3.4	2.5-4.0
Global end-diastolic volume (ml/m2)	713	680-800
Extravascular lung water index (mL/kg)	10.4	<10
Pulmonary vascular permeability index	4.1	<3
Stroke volume variation (%)	12	<13
Pulse pressure variation (%)	11	<12
Median arterial pressure (mmHg)	66	70-105
Central venous pressure (mmHg)	4	2-6
Sistemic vascular resistance index (dyn*s/cm5*m2)	1304	1.800-2.400

Fig. 56.2 Obtained values with advanced hemodynamic monitoring by pulse wave analysis calibrated by transpulmonary thermodilution (PiCCO® system) and their normal range

56.3 Differential Diagnosis

The differential diagnosis included intoxication by substances that have a mitochondrial toxic effect, due to the findings obtained in the point-of-care blood analysis from arterial and central venous catheters.

The first substance we suspected of was cyanide, although it is not an easily available substance for a patient who is admitted to a convalescent hospital. Even so, we screened for all toxicants for which determination was available at our center, either in blood or urine, with all results being negative except for opioids and benzodiazepines (used as analgesics and hypnotics, respectively). We also contacted the reference center for toxicology in Catalonia to carry out a chromatographic analysis of other possible substances that were not available in our center laboratory, the result of which was also negative.

We initially ruled out any substances that cause methemoglobinemia since the methaemoglobin determination was within normal limits in the point-of-care blood analysis. Moreover, other substances with mitochondrial toxic effect, such as carbon monoxide, was initially ruled out since our point-of-care blood gas analysis showed a carboxyhemoglobinemia of 3.2%. Finally, toxic alcohols, such as methanol or etilenglicol, were also excluded as plasmatic osmolarity was normal.

56.4 Treatment

The treatment we carried out was merely supportive, with increasing need of vasoactive drug support and with no improvement of metabolic disturbances.

We also initiated continuous renal replacement therapy with a total dose of 30 mL/Kg/min (25% dialysis, 75% convection) not only for the acute kidney injury

and anuria shown by the patient but also to try to remove an unknown but potentially dialyzable toxic substance such as methanol or etilenglicol, although a normal plasmatic osmolarity made these etiologies less likely.

Under suspicion of cyanide poisoning, we contacted the Burn Unit at our hospital and empirically administered hydroxocobalamin 5 g intravenously so it could bind to cyanide and reduce its toxicity by several mechanisms, which will be explained during the discussion of the present clinical case report.

56.5 Evolution, Outcome, and Follow-Up

After administration of hydroxocobalamin, a marked improvement in oxygen utilization could be observed, reflected in a decrease in the SvO_2 to normal values of 65–70%. The difference between the CaO_2 and CvO_2 widened (15.5 and 11.3 mL/dL), and the oxygen extraction rate increased to normal values of 27.1%.

Despite the improvement in oxygen extraction, the patient showed a continuous worsening in metabolic acidosis with sustained hyperlactatemia (>20 mmol/L), accompanied by progressive clinical deterioration and organ failure.

The patient required increased hemodynamic support with noradrenaline up to 1.2 mcg/kg/min, showing a distributive shock pattern without predictors of volume response, so vasopressin was started at 0.03 Ui/min. Subsequently, over the next few hours, the pattern of shock changed to a mixed cardiogenic and distributive shock, so dobutamine was started up to a dose of 15 mcg/kg/min and vasopressin was increased to full doses (0.06 UI/min). This clinical worsening complicated the tolerance to continuous renal replacement therapy, which had to be discontinued.

In addition, pulmonary edema was observed, which was clinically accompanied by worsening of oxygenation (PaFi 75 mmHg) despite optimization of mechanical ventilation. Due to the hemodynamic situation and the probable futility of the treatment, it was decided not to perform prone positioning.

The patient died 13 h after admission to the ICU.

Unfortunately, we were unable to determine the etiological toxicant. As there were clear indications of a violent death, the court was notified, and all postmortem investigations were kept confidential and were disclosed only to members of the court and family members. Although we contacted the family, they refused to provide information on the etiology of the condition.

56.6 Discussion

The main suspected etiological toxicant was cyanide (CN), which could not be finally proven. The most frequent route of CN intoxication is oral ingestion as a suicide attempt, poisoning, or terrorist attack. CN is converted to hydrocyanic acid (HCN) in the acidic environment of the stomach and rapidly absorbed [1]. Another less frequent route is inhalation during a fire, in the form of HCN produced by the combustion of common household substances, mainly plastics [2].

The body has metabolic pathways to eliminate CN ingested in small amounts in specific foods (add examples), but these pathways are rapidly depleted at high CN concentrations. The most relevant is conversion to thiocyanate, a nontoxic compound easily excreted in the urine. Another one is binding to hydroxocobalamin [1, 2].

CN has a high affinity for ferric iron ion (Fe3+), which is present in multiple intracellular enzymes, such as cytochrome C oxidase, which belongs to complex IV of the mitochondrial electron transport chain (METC). Upon binding, it blocks its function, which is to regenerate the reducing power of the METC. This blockage renders the METC and thus aerobic metabolism useless, forcing the cell to switch to anaerobic metabolism, which is less efficient and leads to high lactate production, metabolic acidosis, and cell death [1, 2].

One of the typical signs of CN intoxication is arterialization of venous blood, as we saw in our patient and has been reported in the literature [3]. Despite adequate oxygen delivery, the oxygen extraction rate is very low, and typical parameters of anaerobic metabolism are present [1–3]. Diagnosis is difficult as the determination of CN is slow and not available in most centers. Therefore, the diagnosis is usually *ex juvantibus* or at autopsy [1, 2].

Treatment is mainly supportive. Pure oxygen supplementation is recommended hypothesizing a faster CN removal with increased oxygen delivery and consequently higher cytoplasmic oxygen concentration. The use of hyperbaric therapy has been proposed, although its use is controversial. Hydroxocobalamin infusion aims to enhance the second metabolic pathway, with acceptable tolerance and few adverse effects. Another antidote, currently less used, is known as the three-drug antidote. Firstly, the amyl nitrite beads are broken and the vapor produced inhaled. Immediately afterward, 300 mg of sodium nitrite are infused intravenously. Both substances produce methaemoglobin, whose ferric ion has a greater affinity for CN than that of cytochrome C oxidase, forming cyanmethemoglobin. Finally, thiosulfate is infused, which acts as a sulfur donor, combining with cyanmethemoglobin and producing thiocyanate, which is excreted via the urine. This second antidote has more serious adverse effects such as hypotension with sodium nitrite infusion and the creation of methaemoglobin, which can further compromise oxygen delivery to the tissues [1, 2].

Take-Home Messages

- A high central venous oxygen content and, therefore, a high central venous oxygen saturation are a sign of decreased oxygen consumption.
- Mitochondrial dysfunction is the most common cause of oxygen underconsumption and can be caused by several diseases.
- Cyanide is the most common exogenous substance that can cause mitochondrial dysfunction.

Summary

Mitochondrial toxicity causes dysoxia, or abnormal tissue oxygen utilization. To maintain energy production, cells are forced to switch to the less efficient anaerobic metabolism that ultimately leads to cell death, multi-organ dysfunction, and death. Cyanide is one of the most common mitochondrial toxicants.

We present a patient who presented with decreased level of consciousness and distributive shock of unclear etiology, in whom the main diagnostic suspicion was poisoning by a mitochondrial toxicant. The suspicion was raised after obtaining bright red venous blood with a high oxygen content. Hydroxocobalamin was administered, with an improvement in cellular oxygen consumption, although the hyperlactemic metabolic acidosis and multi-organ dysfunction situation could not be reversed, causing the patient's death.

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The Best Clinical Cases in Severe Inflammatory Disorders

Contents

Immune-Inflammatory Disorders in the ICU

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Contents

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Learning Objectives

- Recognize the importance of immune-inflammatory disorders in intensive care.
- Describe the epidemiology, clinical features, and complications of the main immune-inflammatory disorders that may lead to admission to the ICU.
- Understand the diagnostic workup of immune-inflammatory disorders in critical illness.
- Summarize the major principles guiding the management and treatment of immune-inflammatory disorders in the ICU, including the use of specific drugs and supportive care.

57.1 Introduction

Critical illnesses are frequently associated and complicated by immune-inflammatory disorders, either as preexisting comorbidities or new diseases exacerbated by critical care status [1]. Systemic manifestations of preexisting immune-inflammatory disorders can become serious life-threatening conditions, thus requiring intensive care unit (ICU) support. Most patients with immune-inflammatory diseases who refer to emergency department have a rheumatologic disease, and one-third of them need ICU admission. Despite the relatively younger age of these patients, the mortality rate has been reported to be as high as 40–60%, which is higher than that of the general ICU population [2, 3]. Several immune-inflammatory diseases can deteriorate needing admission to ICU, including rheumatoid arthritis, systemic lupus erythematous, and systemic vasculitis [4]. Other less prevalent conditions include antiphospholipid syndrome, dermatomyositis, and neuromuscular disorders. Although a subset of patients has a history of immune-inflammatory disorders before they are admitted to the ICU, almost 20% of them are newly diagnosed with immune-inflammatory or rheumatologic disorders in the ICU [4]. Despite the high rates of ICU admission and mortality, the literature on immune-inflammatory disorders in the ICU is poor. The most common causes of ICU admission among critically ill patients with immune-inflammatory disorders include development of new disease-related manifestations, infections secondary to immunosuppressive treatment, adverse effects of disease-modifying drugs, and acute critical compromise exacerbated by the underlying immune-inflammatory disorders [5].

Apart from these systemic immune-inflammatory disorders, hyperinflammatory response to a trigger such as sepsis, infection, or malignancy may occur and result in widespread clinical consequences. The trigger leads to a strong and destructive immunologic response that mimics sepsis [6]. Hyperactivation of macrophages, natural killers, and T cells and production of over 100 inflammatory cytokines lead to cytokine storm and hyperinflammation. Recently, these conditions related with hyperinflammatory response have been identified as secondary hemophagocytic lymphohistiocytosis, macrophage activation syndrome, or cytokine release syndrome [7]. Patients suffer from recurrent fever, cytopenia, liver dysfunction, and sepsis-like syndrome that may rapidly progress to terminal multiple organ failure. These symptoms may be due directly to cytokine-induced tissue damage or acute-phase physiological changes or may result from immune cell-mediated responses [8]. Patients can progress rapidly to disseminated intravascular coagulation with either vascular occlusion

or catastrophic hemorrhages. Many patients have respiratory symptoms, including cough and tachypnea, that can progress to acute respiratory distress syndrome (ARDS), with hypoxemia, that may require mechanical ventilation. Dyspnea, hypoxemia, hypotension, hemostatic imbalance, vasodilatory shock, and death occur in patients with severe disease. The combination of hyperinflammation, coagulopathy, and low platelet counts places patients with cytokine storm at high risk for spontaneous hemorrhage [9].

Treatment strategies of systemic immune-inflammatory disorders are based on the type of the diseases and aim to downregulate an overreactive immune system and to control the clinical manifestations of these disorders. Steroids, disease-modifying antirheumatic drugs, nonsteroidal anti-inflammatory drugs, and the new biologic disease-modifying agents are usually used for treatment. However, in critically ill patients, due to possible unresponsiveness of these agents and requirement of more immediate response to preserve the patient's life, alternative therapeutic strategies such as therapeutic plasma exchange and intravenous immunoglobulins are usually applied by intensivists [2].

The general treatment strategies of hyperinflammatory response to a trigger involve supportive care, control of the underlying diseases, and elimination of triggers by targeted immunomodulation or nonspecific immunosuppression. Although in many studies, immunomodulation by neutralization of elevated cytokine levels in the circulation with an agent (anti-interleukin [IL]-6, antitumor necrosis factor [TNF], anti-interferon-γ or anti-interleukin-1β antibody) has promising results, it may not always be effective due to potentially elevated cytokine levels in tissue and some serious side effects of immunomodulatory agents [9].

The aim of this chapter is to briefly characterize and discuss the prevalence, pathophysiology, diagnosis, and treatment of immune-inflammatory diseases that can affect critically ill patients. Following this chapter, four clinical cases about rare diseases in critical care setting, such as systemic capillary leak syndrome, hemophagocytic lymphohistiocytosis, adult-onset Still's disease, and other more common such as myasthenia gravis, will be discussed.

57.2 Systemic Capillary Leak Syndrome

57.2.1 Introduction

Systemic capillary leak syndrome (SCLS) is defined as an increased capillary permeability to proteins which lead to the passage of protein-rich fluid from the intravascular to the interstitial space [10]. Sepsis is the most common disease associated with SCLS, although other disease including the idiopathic systemic capillary leak syndrome or Clarkson's disease, engraftment syndrome, differentiation syndrome, the ovarian hyperstimulation syndrome, hemophagocytic lymph histiocytosis, viral hemorrhagic fevers, autoimmune diseases, snakebite envenomation, and ricin poisoning can be identified. Drugs including some interleukins, monoclonal antibodies, and gemcitabine can also cause capillary leak syndrome. SCLS in patients with sepsis has a mortality rate as high as 30% in acute disease. After the advent of new prophylactic

therapies such as intravenous immunoglobulins, SCLS mortality has decreased from 80% to 15% [11]. Despite increasing interest in SCLS, the literature is very poor, and this entity remains a diagnostic niche. In addition to high mortality, frequent misdiagnosis, unclear pathophysiology, and difficult care for severe cases are common and make the management of this syndrome challenging.

57.2.2 Pathophysiology

SCLS manifests with the same underlying pathophysiologic abnormality regardless of the causative mechanism, which consists in an increase in capillary permeability to proteins [12]. As a result, there is a loss of protein-rich fluid from the intravascular to the interstitial space. In all cases, release of cytokines and cytokine storm are believed to be the underlying causes of capillary leak. In SCLS, the endothelium is altered, due to the lack of integrity between endothelial cells, making the endothelial barrier between the intravascular and interstitial spaces weak. In normal conditions, endothelial cells bind to neighboring cells through adherent junctions and tight junctions. Upon inflammatory stimuli, vascular endothelial cadherin is internalized, thus causing weakness of the adherent junctions and increased permeability while preserving the endothelial architecture [13]. In case of greater inflammatory stimuli, the architecture is reverted resulting in endothelial cell separation with gap between cells and increased permeability [14]. At systemic level, this manifests with possible diffuse edema and consequent heart-lung and multi-organ failure.

57.2.3 Diagnosis

Clinical diagnosis is challenging since initial symptoms are unspecific. SCLS can lead to a sepsis-like syndrome which is characterized by diffuse pitting edema, exudative effusions from serous cavity, noncardiogenic pulmonary edema, hypotension, and possible shock with high potential for multi-organ failure. Diffuse severe edema, fluid overload, and hypovolemia can be associated with hemoconcentration and hypoalbuminemia. Therefore, the early identification of the underlying disease associated with SCLS assumes a pivotal role. Depending on the underlying cause, diagnostic tests can be more, or less, invasive including also radiological imaging, ultrasound, as well as specific laboratory and microbiological tests.

57.2.4 Management and Therapy

Given the small number of patients with capillary leak syndrome in the literature, there is a lack of sufficient evidence to guide intensive care treatment. Critical care management of SCLS includes hemodynamic stabilization, accurate fluid management, treatment of underlying cause, and prevention of complications. Fluid management is the most critical element in the treatment of capillary leak syndrome. The hemodynamic profile of patients with capillary leak can vary from stable blood pres-

sure with intact perfusion and fluid overload to fulminant hypovolemic shock [15, 16]. The ongoing albumin loss from the vascular space limits the effectiveness of albumin for volume expansion. In case of hypotension, vasopressors can be administered although they are expected to be less effective given that intravascular volume depletion underlies the shock in these patients [17]. Patients with SCLS are at high risk of noncardiogenic pulmonary edema during fluid resuscitation. In some patients, pulmonary edema develops after the blood pressure has stabilized due to the return of interstitial fluid to the intravascular space. Therefore, a fluid-restrictive strategy is advocated during volume resuscitation. After the administration of a fluid bolus, the reassessment of the intravascular volume and pulmonary status can be achieved with further intravenous fluid administration. Upon stabilization of hemodynamic, diuretic therapy can be initiated to prevent the development of pulmonary edema [18]. In patients who present with a stable hemodynamic but show signs of fluid overload, loop diuretics can be considered as first-line therapy. The combination of albumin and diuretics has been successful for removing volume [19, 20]. Acute kidney injury is a possible complication of SCLS; thus, patients may require renal replacement therapy. In those with hemodynamic instability, continuous renal replacement is favored over intermittent hemodialysis [20].

Steroid therapy has demonstrated efficacy because of the suppression of hyperinflammatory cytokine-mediated immune response [21]. Finally, intravenous immunoglobulin administration is currently the most promising therapy for SCLS. Intravenous immunoglobulins should be initiated as soon as possible in a patient suspected of SCLS using a dose of 2 g/kg monthly [22].

57.3 Hemophagocytic Lymphohistiocytosis

57.3.1 Introduction

Hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome (HS) is a rare life-threatening condition which results from an impairment of T cells and natural killer cell functions leading to a dysregulated inflammatory response with massive release of pro-inflammatory cytokines and possible acute multi-organ failure [23]. HLH can be classified as primary or secondary. Primary HLH is usually known as familial HLH (F-HLH), which is caused by genetic mutations in a homozygous or compound heterozygous pattern, resulting in altered function of cytotoxic T cells and natural killer cells. Secondary or acquired HLH is triggered by external stimuli such as infections, malignancy, rheumatologic disease, post-allogeneic hematopoietic stem cell transplantation, drug hypersensitivity, or other underlying causes. The most common infectious agent associated with HLH is the Epstein-Barr virus (EBV) [24].

Patients with HLH who are admitted to the ICU show a 57% mortality rate, regardless of HLH etiology. Factors independently associated with outcome included age, hemophagocytosis in bone-marrow aspirates, organ failure at admission, and worsening organ failure during the ICU stay.

57.3.2 Pathophysiology

In the primary form of HLH, an initial immune defect related to a genetic anomaly, usually involving the perforin pathway, can affect the cytotoxic pathway leading to an inability to clear the antigenic stimulus. This is followed by an inflammatory response, which leads to uncontrolled hypercytokinemia with sustained macrophage activation and tissue infiltration. Acquired HLH is usually related to an underlying condition involving spontaneous cytokine storm [25].

57.3.3 Diagnosis

The clinical hallmark of diagnosis is the presence of high fever (39–40 °C) associated with pan-/bi-cytopenia [25]. Fever can be persistent (1–4 weeks) and alert the physician if an infective cause has been ruled out. HLH should be accounted as a possible differential diagnosis for patients admitted to the ICU with septic shock and preexisting fever and asthenia for several weeks [25]. Splenomegaly is a possible manifestation in up to 75% [26]. Biochemical anomalies accompany this syndrome, including high ferritin and triglycerides levels. High levels of ferritin should exclude as differential diagnosis other causes like sepsis, blood transfusions, and hepatitis, although in HLH ferritin levels can be over 2000 g and be associated with other very informative symptoms [26]. If the clinical and biological suspicion of HLH is high, bone-marrow aspiration should be considered for diagnosis. Hemophagocytic figures are very frequent but not constant. The lack of hemophagocytic figures does not preclude the diagnosis of HLH [27]. In case of multiple organ failure, sepsis, and blood transfusions, hemophagocytic figures can be observed without diagnosis of HLH. Diagnostic criteria include the H Score typically used in secondary HLH in adult population [28]. Additionally, the biological marker soluble CD25 seems to be quite specific and may be associated with hemophagocytic activity, but it is not routinely available [29].

57.3.4 Management and Therapy

HLH patients can require ICU admission and critical care. Coagulation disorders should be carefully assessed [30], and platelet and plasma transfusions may be required. Particular attention is required when biopsies are necessary for diagnosis. As the symptoms of HLH may be indistinguishable from those of septic shock, broad spectrum antibiotics and/or antifungal drugs should be preventively started at the time of presentation [30]. Supportive care can include mechanical ventilation or renal replacement therapy in case of renal deterioration or massive fluid overload.

Reduction of inflammation can be obtained by decreasing cytokine levels using steroids or etoposide. Etoposide acts by depleting the activated T cells, which represent the stimulus for activation of macrophages. Dose of etoposide varies between 150 and 200 mg/kg and adapted to kidney or liver dysfunction [31]. High-dose intravenous polyvalent immunoglobulins may improve the symptoms, especially in the case of viral infections, but associated with steroids seem to produce better response. Treatment should be started early at symptom onset. Untreated HLH can lead to multi-organ failure and death [31].

57.4 Myasthenia Gravis

57.4.1 Introduction

Myasthenia gravis (MG) is an autoimmune disease characterized by muscle weakness and fatigability [32]. MG is caused by harboring antibodies to the nicotinic acetylcholine receptor (AchR) [33]. A possible variant of MG is muscle specific kinase (MuSK) antibody-positive that is typical of younger female [33, 34]. In around 10% of cases, MG is associated with malignant thymoma, a rare epithelial tumor [35].

The prevalence of MG is around 1–40/100,000 person and is more frequent in younger female (aged less than 40 years old) or older male (aged more than 60 years old). Around 50% of cases present fatigue of the extraocular muscles (asymmetric ptosis), and in around 20% of them, the disease does not progress [36]. However, in most patients, the disease will progress systemically to other muscles, causing head drop, dysphagia, dysarthria, limb weakness, and diaphragmatic dysfunction. When MG manifests in older age, the probability of complete remission is lower than in younger patients, and mortality is higher. Older patients often develop refractory diplopia and generalized weakness and are more susceptible to secondary effects of immunosuppressive therapies like infections, osteoporosis, and other complications [37].

The course of the disease is generally subacute or rapidly progressive, with possible "myasthenic crises" and rapid involvement of the respiratory muscles with the need of emergency and intensive care [35]. Around 10–20% of patients with MG require ICU admission, complicated by systemic infection, and need ventilatory support. In the latest years, MG patients who required emergency critical care showed a decline of mortality from 40% to 5%, thanks to novel medications and appropriate ventilatory setting [38, 39]. However, in hospitals where a specialized neurocritical ICU is not available, the mortality rate remains up to 30% [40].

57.4.2 Pathophysiology

MG is an autoimmune disorder caused by autoantibodies directed against the AchR, thus reducing the number of functional postsynaptic receptors located in the muscle cell membrane [35]. The response of the neuromuscular junction is impaired, thus requiring a higher percentage of AchR to be occupied by acetylcholine. Once all receptors are occupied, the transmission of the signal is blocked, and the amplitude of the action potential lowered, resulting in weak contraction of few muscles. At this point, the postsynaptic membrane tends to degenerate [41]. Variability can be observed in those cases which present antibodies directed against the MusK or LRP4 protein, which are both involved in AchR clustering on the muscle cell membrane [41].

Lymphoid follicular hyperplasia which stimulates T lymphocytes and thymic B cells to produce AchR antibodies is also possible, especially seen in patients younger than 60 years old, females, and those with HLA-DR3 positivity. This is also driven

by immunologic mechanisms that start in the thymus, where the myeloid cells share epitopes with the AchR. Dendritic cells may express HLA epitopes that can play a role in the presentation of the antigen in AchR, similarly to myoid cells [41].

57.4.3 Diagnosis

MG is commonly diagnosed by clinical examination. MG patients can manifest fatigability (90 seconds' upgazed, lateral gazed, 60 s head rise from the flat, 90 s arm abduction, and 90 s leg flexion and knee extension). The gold standard for the diagnosis is the Tensilon test with the administration of 2 mg of edrophonium followed by 8 mg intravenous. Edrophonium can cause bradycardia; thus, the test should be performed under electrocardiogram monitoring. The "ice pack test" can be performed applying external cold on the eye observing transient improvement of muscular contraction [41].

Electromyography represents another important test for the diagnosis of MG by stimulating train of 6 with 3-second repetitive and observing a 10% decrement of the action potential of muscles, sometimes followed by facilitation [41]. Laboratory biomarkers of MG include AchR, anti-MuSk, and anti-LRP4 antibodies. Additionally, anti-striational antibodies such as anti-titin, anti-ryanodine receptor, and anti-Kv1.4 are associated with thymoma [42].

57.4.4 Management and Therapy

The management and treatment of MG can be either supportive or pharmacological, depending on the phase of the disease and the clinical response. Each possible pharmacological treatment has some strengths and pitfalls. Cholinesterase inhibitors such as pyridostigmine are key pharmacological agents for improvement of neuromuscular transmission. However, its effect is lost if antibodies persist. In general, the treatment of MG usually starts with pyridostigmine (30 mg, titrated up to 60 mg q6/day since the effect lasts around 4–5 h) or, in alternative, neostigmine. Higher doses can cause a cholinergic crisis and are not recommended. Possible side effects include gastrointestinal manifestations and hypersecretions that can be easily managed through the administration of propanthelines 15 mg and glycopyrrolate. This therapy is more effective when associated with early immunosuppression. Within this context, intravenous immunoglobulin (IVIg) treatment showed benefits as well as the administration of steroids. Prednisolone or prednisone constitutes the main immunomodulatory therapy in the long-term management of patients with MG. Typical strategy includes prednisolone 10 mg daily, increasing by 10 mg every forth dose up to 50–100 mg daily for 5–6 months [43].

Another solution can be the surgical remotion of thymoma with minimally invasive thymectomy, thus limiting the source of autoantibodies. Thymectomy is suggested in the initial phase of the disease; otherwise, antibodies can be spread from germinating centers to systemic sites being produced outside the thymus.

Other drugs include azithromycin, azathioprine, mycophenolate mofetil, cyclosporine, and tacrolimus. All these drugs are constrained by high costs and potential detriment effects with longer use [44]. For those patients who are refractory to stan-

dard treatments (around 20%), rituximab, a monoclonal antibody acting through the blockage of B cell functions and T cell stimulation, can be considered. Other newly promising therapies can be considered, including eculizumab, efgartigimod, and bortezomib, but further research is warranted to confirm their efficacy and tolerability [45].

Intravenous immunoglobulins (IVIg) and plasma exchange represent rescue options in patients who have failed standard treatments or rapidly deteriorate. IVIg has the disadvantage of a short-term effect but can be administered without admission to a hospital, while plasma exchange or immunoadsorption needs admission to the hospital or ICU with central venous access. Possible complications include infections, coagulopathy, and air embolism [46].

Supportive treatments play a key role for patients with MG. Patients with MG who are rapidly deteriorating for respiratory mechanics and gas exchange should be carefully evaluated and rapidly admitted to an ICU. The most common reason for ICU admission is a myasthenic crisis, complicated by respiratory failure, thus requiring endotracheal intubation and mechanical ventilation in 30% of cases. Breathing patterns and the central ventilator drive can be altered in patients with mild or moderate MG, as well as the respiratory system compliance and chest wall, accompanied by alveolar collapse and atelectasis [47].

Typical signs of deterioration and respiratory failure include inability to lie flat, impossibility to complete a sentence without breath, use of auxiliary respiratory muscles, decreasing ability to count loud in one breath, or paradoxical abdominal movement. Therefore, a complete clinical evaluation of the diaphragmatic function and thickness is pivotal, since an altered diaphragmatic and intercostal muscles' function can affect vital capacity, as well as airway clearance and expiration. Within this context, the "20/30/40″ rule has been proposed for patients with MG at risk of deterioration and in need of endotracheal intubation and ICU admission. Recently, novel machine learning-based decision tree methods have been developed to identify the MG patient earlier, who can benefit from ICU admission. The C5.0 method seemed the most promising for predicting clinical deterioration and need for ICU admission [47, 48].

ICU management of MG does not include only mechanical ventilation for muscle weakness but should start from a comprehensive evaluation of multi-organ function, although the prevention and management of airway collapse and the inability to clear secretions revest a pivotal role. Advanced hemodynamic monitoring and appropriate fluid therapy, nutritional support, treatment of infections, and other complications should be pursued. Additionally, an appropriate program of respiratory physiotherapy and rehabilitation with a proper cough management (i.e., cough assist devices, recruitment maneuvers, manual or mechanical insufflation-exsufflation) is essential in this patient population [44]. The respiratory function can be supported initially by noninvasive mechanical ventilation using pressure support, but in case of deterioration, an artificial airway via endotracheal intubation and mechanical ventilation should be pursued. At some point, a tracheostomy cannula can be necessary to maintain airway patency and to guarantee manual aspiration of secretions while limiting the damage of a prolonged endotracheal tube. Mechanical ventilation should be set according to the lung protective ventilator strategy [49].

Weaning from the ventilator can be initiated once the patient reaches the criteria for considering a spontaneous breathing trail (◘ Fig. 57.1). Weaning methods can

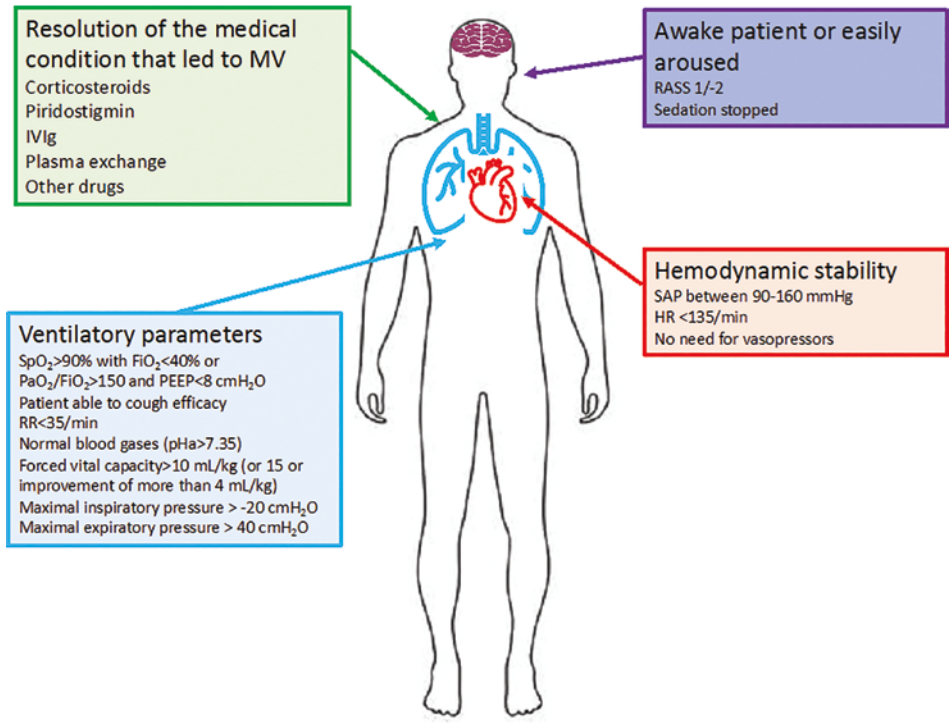

Fig. 57.1 Criteria for initiating a spontaneous breathing trial in patients with myasthenia gravis. *Modified from Weiss* et al. *"Should We Assess Diaphragmatic Function During Mechanical Ventilation Weaning in Guillain–Barré Syndrome and Myasthenia Gravis Patients?" Neurocritical care. 2021. 34: 371–374. FVC* Forced vital capacity, F_IO_2 Inspired oxygen fraction, *MV* Mechanical ventilation, PaO_2 Partial oxygen arterial pressure, *PEEP* Positive end-expiratory pressure, *PSV* Pressure support ventilation, *RASS* Richmond assessment sedation scale, *RR* Respiratory rate, *HR* Heart rate, *SBT* Spontaneous breathing trial, SpO_2 Pulsed oxygen saturation, *SAP* Systolic arterial pressure

include bilevel airway pressure support, a T piece, intermittent mandatory ventilation, assisted ventilation, or neurally adjusted ventilatory assist [49]. In case of impossibility to achieve the liberation from the mechanical ventilator, a domiciliary ventilatory strategy can be considered [49].

57.5 Adult-Onset Still's Disease

57.5.1 Introduction

In 1897, George Still reported 22 children affected by systemic onset juvenile idiopathic arthritis [50]. Bywaters et al. described the first series of adult-onset Still's disease (AOSD) in 1971, reporting 14 adult patients with the same symptoms of pediatric Still's disease such as fever, skin rash, and polyarthritis [51]. AOSD is a multisystemic autoinflammatory disorder of unknown etiology and usually affects young adults and has poor prognosis. It is typically characterized by high fever, poly-

arthralgia, skin rash, sore throat, leukocytosis, and hyperferritinemia. Due to lack of studies on AOSD, the epidemiologic data, the pathophysiology of the disease, and management strategies are still not fully evaluated and understood [51, 52].

The median age at AOSD diagnosis is nearly 36 years, and the disease has a bimodal peak at the age 15–25 and 36–46 years. However, old age onsets even after 80 years have also been reported [52]. In some case series, up to 70% of the patients are women, but AOSD is considered equally distributed between sexes [52]. The prevalence rates range from 1 to 34 cases per 1 million people, and its incidence has been reported between 0.16 and 0.4/100000 people [53]. Although AOSD has severe complications such as macrophage activation syndrome (MAS), disseminate intravascular coagulation (DIC), and diffuse alveolar hemorrhage, there has been no study on AOSD prevalence in ICU. One previous study analyzed 20 patients with AOSD requiring ICU admission due to AOSD related organ failure and reported 10% ICU mortality [54].

57.5.2 Pathophysiology

The etiology of AOSD still remains unclear, whereas various mechanisms contributing to the pathogenesis of AOSD have been described.

AOSD is defined as a multigenic disorder. Although familial trend has not been reported, some associations between AOSD and human leukocyte antigens (HLAs) (HLA-B17, HLA-B18, HLA-B35, HLA-DR2, and HLA-DR4) have been reported [55].

Infections especially viral infections have been suspected as a potential trigger of AOSD due to the similar symptoms between them. Many cases of infectious pathogens in AOSD patients including rubella virus; Ebstein-Barr virus; cytomegalovirus; influenza virus; echovirus; parainfluenza virus; hepatitis A, B, and C viruses; adenovirus; coxsackievirus; mycoplasma pneumonia; chlamydia pneumonia; and *Yersinia enterocolitica* have been reported. However, no unique pathogenic trigger has been clearly defined due to lack of cohort studies [56].

The activation and amplification of inflammation, characterized by a cytokine storm, is the hallmark of AOSD. Inflammation is mainly driven by innate immune cells but also adaptive immune cells. Macrophage and neutrophil activation play a major role in the pathogenesis of AOSD [56]. Neutrophil activation, natural killer (NK) cell deficiency, T cell imbalance, and deficient resolution of inflammation are the other underlying causes and mechanisms of hyperinflammation in AOSD patients.

57.5.3 Diagnosis

AOSD symptomatic triad is typically fever, joint pain, and maculopapular salmon-pink evanescent skin rash. Fever occurs in up to 100% of the patients. It typically spikes daily or twice daily. Joint pain is the most common symptom (70–100%). Arthralgia and arthritis involve predominantly the wrists, the knees, and the ankles. Up to 80% of the patients' skin rash appears. Myalgia, splenomegaly, lymphadenopathy, sore throat, hepatomegaly, pericarditis, abdominal pain, and pleurisy are

Table 57.1 Yamaguchi's AOSD diagnostic criteria

Exclusion criteria: infectious, autoimmune, autoinflammatory, and neoplastic diseases	
Major criteria	**Minor criteria**
Fever >39 °C, intermittent, 1 week or longer Arthralgia >2 weeks Typical rash Leukocyte >10,000/mL (>80% neutrophil)	Sore throat Lymphadenopathy and/or splenomegaly Liver abnormalities Negative ANA/RF
Five criteria with at least two majors	

the other signs and symptoms of the disease. Common serious complications of AOSD which usually require ICU admission are listed below.

MAS is the most severe complication of AOSD with a mortality rate of 10–41% [51, 57]. Physicians should be alerted by the change of fever pattern to a non-remitting pattern for MAS. Hepatosplenomegaly and histopathological evidence of hemophagocytosis by activated macrophages in the bone morrow are the characteristic features of MAS [58]. Activation of coagulation factors may lead to DIC during disease course. Non-remitting high fever and purpuric or petechial rash are the main characteristics [59].

Pulmonary involvement is seen in up to 53% of the AOSD cases with the most common pulmonary diseases being pleural effusion and pulmonary infiltrates. Diffuse alveolar hemorrhage and pulmonary hypertension are life-threatening pulmonary complications.

In AOSD patients, other serious complications are aseptic meningitis, thrombotic microangiopathy, and fulminant hepatitis [60].

Leukocytosis, neutrophilia, thrombocytosis, increased C-reactive protein, erythrocyte sedimentation rate, and moderate rise in liver enzymes are common. Serum ferritin levels are usually higher than other autoimmune, inflammatory diseases, and fivefold increase of serum ferritin levels is suggestive of AOSD diagnosis and prediction of MAS occurrence [60].

AOSD is a clinical diagnosis and requires exclusion of potential mimickers including infectious, autoimmune, autoinflammatory, and neoplastic diseases. Although different diagnostic criteria have been developed for diagnosis, Yamaguchi's criteria are the most sensitive (93.5%) (Table 57.1) [61].

57.5.4 Management and Therapy

As there have been no prospective double-blind randomized trials in management of AOSD, current management strategies stem from small retrospective case series and remain empirical. Corticosteroid therapy is considered as a first-line therapy and should be started at a dosage of 0.5–1 mg/kg/day. If severe visceral involvement and/or MAS occur, intravenous high-dose corticosteroids may be considered. Improvement in clinical situation occurs a few days after initiation of corticosteroids [62].

Methotrexate (MTX), which is commonly used as a second-line therapy, has steroid-sparing effect. In a previous study, after adding MTX, complete remission

was observed in 69% of patients, and 39% of patients discontinued corticosteroids [63]. Hydroxychloroquine, intravenous immunoglobulin, and/or cyclosporine A may be considered in MTX unresponsive patients.

Refractory AOSD is identified as resistance disease to first-line and second-line therapies. Biological agents may be used for those patients. A recent meta-analysis showed that biological agents can lead to complete remission in most AOSD patients [64]. Refractory AOSD has been classified into two different subsets according to clinical features of diseases: "systemic AOSD" with high fever, high C-reactive protein, and liver enzymes and "rheumatic AOSD" with steroid resistant arthritis and low ferritin levels. IL-1 antagonists (anakinra, canakinumab, and rilonacept) and IL-6 antagonist (tocilizumab) may lead to better response, whereas TNF-α blockers (infliximab, etanercept, and adalimumab) should be used as first treatment option in patients with refractory rheumatic AOSD [64].

Take-Home Messages

- Critical illnesses are frequently associated and complicated by immune-inflammatory disorders, either as preexisting comorbidities or new diseases exacerbated by critical care status.
- Systemic manifestations of preexisting immune-inflammatory disorders can become serious life-threatening conditions, thus requiring ICU support.
- Diagnosis is not difficult with acute exacerbation of chronic disease, but it is challenging when newly and not previously diagnosed. Immune-inflammatory diagnostic tests and specific panels of biomarkers are suggested.
- Steroids, disease-modifying antirheumatic drugs, nonsteroidal anti-inflammatory drugs, and the new biologic disease-modifying agents are usually used for treatment.

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In Case of Severe Hemoconcentration and Hypovolemic Shock, Also Think of Zebras: A Case of Systemic Capillary Leak Syndrome

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Contents

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Learning Objectives

- In case of severe hypotension, hypoalbuminemia, and hemoconcentration, systemic capillary leak syndrome should be part of the differential diagnosis as this has implications for treatment.
- In hypovolemic shock, fluid resuscitation is the mainstay of treatment. However, when hypovolemic shock is due to SCLS, fluid therapy should even be more frequently evaluated as it can exacerbate the most common complication: compartment syndrome, pulmonary edema, and multi-organ failure.
- The muscle compartments should be carefully monitored throughout resuscitation, leading to immediate surgical consultation in case of suspected compartment syndrome.
- Besides fluid resuscitation, there are no established pharmacologic therapies for capillary leak syndrome, although successful treatment with IVIG and in this case combined with imatinib has been described.

58.1 Introduction

Systemic capillary leak syndrome (SCLS), first described by Clarkson in 1960 and also known as Clarkson's syndrome, is a rare disease with only around 260 adult and 14 children reported cases worldwide [1]. SCLS is characterized by increased capillary permeability with loss of protein-rich fluids to the interstitial space, which leads to hypotension, hemoconcentration, hypoalbuminemia, and/or edema. The major complications are compartment syndrome, pulmonary edema, and finally multi-organ failure [2]. As in other causes of hypovolemic shock (aggressive), fluid administration is usually the key therapy; however, this can lead to further deterioration in SCLS and therefore needs to be monitored even more closely.

This clinical case describes a patient with severe hemoconcentration, tachycardia, and hypotension without any edema at presentation. The clinical diagnosis hypovolemic shock was made and fluid resuscitation started, but against expectations this led to further progression of shock and rapid onset of edema in all four extremities causing compartment syndrome.

In general, once (fluid) therapy is started, it is essential to frequently asses the efficacy of applied therapy. When the clinical course is not as expected or patient deteriorates even further, it is of key importance to consider alternative diagnosis. In case of hypovolemic shock and hemoconcentration, SCLS should be in the differential diagnosis. Although SCLS is rare, with this clinical case, we want to create awareness of the disease and possible complications, as this knowledge might speed up the diagnostic process, thereby ensuring appropriate treatment and preventing further complications and long-term morbidity.

Case study

A 50-year-old man presented to his general practitioner with a 1-week history of malaise, epigastric discomfort, and progressive weakness of both his legs since a few hours. His medical background revealed smoking and a past medical history of a cervical herniated disc.

He had no dyspnea, no palpitations, no nausea or vomiting, and no headache or visual complaints and had never measured his temperature. Defecation and miction were normal. He experienced some joint pain for a longer period, as working as an electrician in construction. Family history was positive for neurological disorders, including multiple sclerosis, cerebral bleeding, and transient ischemic attacks.

Hypovolemic shock due to an abdominal aneurysm was suspected, and the patient was transferred to our emergency department. Initial assessment revealed a critically ill man with patent airway, respiratory rate of 22 breaths per minute with use of accessory muscles, normal lung sounds, a saturation of 99 % with 40% oxygen delivery, blood pressure of 75/55 mmHg, a sinus tachycardia of 124 beats per minute, and normal heart sounds. The abdomen was not painful on examination. Patient was alert, and neurologic examination was normal. He had no fever and his skin was dry and cold but showed no abnormalities and no edema.

58.2 Investigations

Fluid bolus therapy was administered before further assessment increasing blood pressure to 100/60 mmHg with a minor reduction in heart rate to 120 beats per minute. ECG showed no abnormalities. Blood and urine cultures were taken. Point-of-care ultrasound (FAST exam) showed no free fluid in the abdomen and a hyperdynamic left ventricle suggesting volume depletion.

Computed tomography (CT) of the chest and abdomen showed no abnormalities, especially no dissection, no aneurysm, and no free air or fluids. Brain CT showed no signs of hemorrhage or other pathology. Laboratory results are shown in ◘ Table 58.1.

Table 58.1 Laboratory results obtained on initial presentation to the emergency department

Tests	Laboratory results	Reference ranges
Sodium	▼ 134 mmol/L	136–146 mmol/L
Potassium	5.5 mmol/L	3.6–4.8 mmol/L
Chloride	104 mmol/L	98–108 mmol/L
CRP	▲ 9 mg/L	<8 mg/L
Hemoglobin	▲ 14.6 mmol/L	8.5–11 mmol/L
Hematocrit	▲ 0.72 L/L	0.40–0.50 L/L
Thrombocytes	▼ 149 × 10^9/L	150–400 × 10^9/L
White blood cells	▲ 13.7 × 10^9/L	4–10 × 10^9/L
Creatinine	▲ 195 µmol/L	64–104 µmol/L
Urea	▲ 11.6 mmol/L	3–7.5 mmol/L
Calcium total	▼ 2.11 mmol/L	2.2–2.6 mmol/L
Albumin	▼ 28 g/L	39–51 g/L
Glucose	8.8 mmol/L	3.9–10 mmol/L
Creatine kinase (CK)	▲ 199 U/L	0–170 U/L
CK-MB	3.9 µg/L	<5 ug/L
Troponin T	0.0014	0–0.0014
Blood gas (venous)		
pH	▼ 7.23	7.35–7.45
pCO2	▲ 8.1 kPa	4.7–6 kPa
pO2	▼ 2.3 kPa	10–13.3 kPa
Bicarbonate	25.7 mmol/L	22–26 mmol/L
Base excess	▼ −3.1	−2 to 3
Lactate	▲ 3.2 mmol/L	<2.2 mmol/L

▲ = above reference range, ▼ = below reference range

58.3 Differential Diagnosis

After evaluating the history, clinical examination, and laboratory and imaging findings, the following differential diagnosis was made (Table 58.2).

Table 58.2 Differential diagnosis and considerations

Differential diagnosis	Diagnostic considerations
Shock	
Hypovolemic shock	
– Fluid loss/ severe dehydration	– Causing hemoconcentration, an elevated lactate level and slightly elevated levels of creatinine kinase, and urea matching prerenal kidney injury. Symptoms as cold and dry skin, tachycardia, hypotension, and a hyperdynamic left ventricle supported this diagnosis. However, anamnesis was negative for decreased intake or fluid loss
– Systemic capillary leak syndrome	– Suggestive for this diagnosis was the remarkably high hemoglobin value combined with hypotension and hypoalbuminemia. However, there was no edema at presentation, possibly because of acute disease course
Distributive shock	
– Sepsis with unknown focus	– However, patient had no fever, clinical assessment revealed no focus for infection, and imaging showed no abnormalities. His skin was cold and dry, possibly matching "cold septic shock" consisting of decreased cardiac output and low systemic vascular resistance; however, echocardiography showed a hyperdynamic left ventricle not fully matching this diagnosis
– Anaphylactic shock	– Tachycardia and hypotension were present, but with no urticaria or other symptoms matching the diagnosis
Cardiogenic shock	– There were signs of shock (hypotension, impaired organ perfusion), however not matching the cardiogenic type since echocardiography was not suggestive of a reduced cardiac index (despite no exact measurements were done) and ECG showed no signs of ischemia
Obstructive shock	– Clinical assessment and echocardiography were negative for pulmonary embolism, pericardial tamponade, and tension pneumothorax
Erythrocytosis	
Primary erythrocytosis	
– Polycythemia vera	– The level of white blood cells was also slightly elevated, but the level of thrombocytes was normal and there was no splenomegaly. This, together with the clinical picture, in which signs of shock were particularly prominent, made the diagnosis polycythemia vera less likely

(continued)

Table 58.2 (continued)

Differential diagnosis	Diagnostic considerations
Secondary erythrocytosis	
– Erythropoietin (EPO) producing tumor	– CT imaging showed no tumors; together with the clinical picture, this diagnosis was unlikely
Hemoconcentration	
– Due to dehydration – Due to systemic capillary leak syndrome	– As mentioned above (see *hypovolemic shock*)

58.4 Treatment

Because of progressive shock with signs of volume depletion (tachycardia, hypotension, dry skin, hyperdynamic left ventricle suggesting low preload, elevated levels of hemoglobin, lactate, creatine kinase, and urea), the patient received a total of 5 L of Ringer's lactate solution in the course of several hours at the emergency department. Noradrenaline infusion was commenced targeting a mean arterial pressure of 65 mmHg ensuring organ perfusion and albumin, hydrocortisone, and ceftriaxone were administered for sepsis e.c.i. Despite fluid therapy, there was an increasing noradrenaline requirement, and hemoglobin and hematocrit levels kept rising (maximum hemoglobin 16.0 mmol/L, reference range 8.5–11 mmol/L, maximum hematocrit 0.78 L/L, reference range 0.40–0.50 L/L), and there was progressive edema of his extremities.

This led to the working diagnosis systemic capillary leak syndrome. Further laboratory tests showed a detectable monoclonal protein IgG kappa, supporting the diagnosis. Patient showed signs of fatigue and progressive respiratory distress and was therefore transferred to the intensive care unit and intubated. Right before intubation, patient started complaining of pain in his legs. Laboratory results showed an increase in creatine kinase levels up to a maximum of 9605 μmol/L (reference range, 64–104 μmol/L). Fluid therapy was stopped, and the surgeon was consulted as compartment syndrome was feared. All extremities were swollen and felt tight, and Doppler signals were absent so urgent fasciotomy was performed on all extremities.

Initiated pharmacologic therapy included imatinib (800 mg per day), a selective tyrosine kinase inhibitor, and IVIG (Nanogam 5%, 1 g per kilogram per day) both with the aim of recovering the vessel wall integrity since this is thought to be the direct pathophysiological feature of SCLS. In addition, therapy with prednisolone

(1 mg per kilogram per day) was started because of its anti-inflammatory properties and calcium carbasalate (a platelet aggregation inhibitor, 100 mg per day) because of the severe hemoconcentration.

58.5 Evolution, Outcome, and Follow-up

In the following days, patient clinically improved with reversal of shock. On day 5, the patient was hemodynamically stable, the imatinib was discontinued, and the prednisolone was tapered off. The same day surgical closure of the fasciotomy wounds took place. On day 7, he was extubated, and 2 days later he was discharged from the intensive care unit to the normal ward. On day 20, he was discharged home, with monthly outpatient appointments for intravenous immune globulin therapy (IVIG) of 2 g per kilogram for 1 day a month during the first year. After that, the IVIG dosage was tapered to 1 g per kilogram monthly. To date, 4 years later, no recurrent episodes of SCLS have occurred.

58.6 Discussion

SCLS is a rare chronic disease which causes recurrent episodes of capillary leakage which may vary in frequency (intervals ranging from days to years), severity (only mild symptoms up to ICU admission and even death), and duration (median duration 3.8 days, range 1–27 days). Up to date, only a few hundred cases have been reported, mostly occurring in middle-aged adults with no sex predominance. Risk factors, including a positive family history, have not yet been identified. The exact incidence remains unknown as it is a diagnosis of exclusion and probably underdiagnosed. Reported mortality rate ranges from 14% up to even 80% in patients who did not receive any maintenance therapy after first diagnosis. Two deaths due to the exacerbation of SCLS associated with COVID-19 have been described [1–4].

Typical symptoms include hypotension, hemoconcentration, hypoalbuminemia, and edema due to increased vascular permeability. In most cases SCLS episodes were preceded by a viral-like prodrome with dizziness, fatigue, and upper respiratory tract infections. The majority of patients with SCLS have a monoclonal gammopathy of unknown significance (MGUS), most commonly the IgG kappa isotype. Exact pathophysiology of SCLS is still unclear, as well as the role and importance of the monoclonal proteins. Therefore, SCLS remains a clinical diagnosis [1, 2]. Management should be focused on stabilizing the patient, restoring perfusion, and effective circulating volume. Fluid administration should be done with an even more cautious approach, as excessive amounts will lead to progressive edema and further hemoconcentration due to the ongoing leakage of protein-rich fluids to the interstitial space, worsening the clinical condition and causing more harm to the patient. For this more advanced monitoring, e.g., using point-of-care ultrasound or cardiac output measurements by thermodilution is advised. Complications of SCLS include hypoperfusion-related multi-organ dysfunction, hypercoagulability due to hemoconcentration and increased viscosity, pleural and pericardial effusions, and massive peripheral pitting edema

resulting in compartment syndrome [1, 2]. In cases of excessive fluid administration and/or progressive edema, be aware that compartment syndrome can develop as increased awareness can lead to early recognition and treatment preventing long-term morbidity. The exact effectiveness of various medical treatments remains unclear, since episodes of SCLS are self-limiting and only observational data exist. Successful therapies have been described in a few cases, including IVIG, theophylline, and tumor necrosis factor-α antagonist infliximab treatment. IVIG has also been successfully used in preventing recurring episodes of SCLS in multiple case series [1, 2, 4]. Imatinib, a tyrosine kinase inhibitor, might also be beneficial on theoretical grounds as it has shown to protect against capillary leakage in different conditions. A recent study showed that treatment with imatinib to attenuate vascular leak in COVID-19 patients shortened duration of mechanical ventilation and reduced mortality [5–7]. The use of imatinib in SCLS was also described in one case report, suggesting effective reversal of vascular leak [8]. During hospital admission, standard therapy includes prophylactic anticoagulation. In case of thrombotic complications, therapeutic anticoagulation therapy should be started [1]. In conclusion, when a patient presents with hypotension, hemoconcentration, hypoalbuminemia, and/or edema and there is no clear initial diagnosis, include SCLS in the differential diagnosis. Though being a rare disease, early recognition might prevent further harm and future episodes.

Take-Home Messages

- Systemic capillary leak syndrome is a rare chronic disease characterized by hemoconcentration, hypotension, and hypoalbuminemia due to capillary leakage; fluid administration may eventually worsen the clinical course.
- Evaluate initiated therapy even more frequently, and keep looking for alternative diagnosis in case of an abnormal course with lack of improvement
- In cases of progressive edema or excessive fluid administration, be aware that compartment syndrome can develop.
- Early recognition and treatment of compartment syndrome is essential as this can prevent long-term morbidity.

Summary

Systemic capillary leak syndrome (SCLS) is a rare disease characterized by recurrent episodes of hypotension, hemoconcentration, and edema due to capillary leakage of protein-rich fluids to the interstitial space. Fluid therapy is the mainstay of treatment; however, this may worsen symptoms leading to organ dysfunction and compartment syndrome in severe cases.

This case report describes a patient who presented with tachycardia, hypotension, and hemoconcentration. Clinical assessment suggested hypovolemic shock and fluid therapy was initiated. Nevertheless, there was progressive clinical deterioration with increasing hemoconcentration and development of edema in all extremities, matching the SCLS diagnosis. Fluid therapy was stopped but compartment syndrome could not be prevented. Fasciotomy was performed and treatment with imatinib, a selective tyrosine kinase inhibitor, and intravenous immunoglobulins (IVIG) was started. After 20 days, the patient was discharged home.

Management of SCLS should be focused on stabilizing the patient and restoring perfusion and volume depletion. Fluid administration should be done with a more cautious approach, as excessive amounts may worsen the clinical condition, causing more harm to the patient. Exact pathogenesis and disease-specific treatment for SCLS remain unclear. Based on pathophysiological grounds, both imatinib and IVIG may be effective in restoring the profound derangements of the vascular endothelium. Several case reports describe the success of IVIG in SCLS, and intermittent treatments may prevent future episodes. In hypovolemic shock with no clear etiology, include SCLS in the differential diagnosis. Early diagnosis of SCLS, frequent evaluation of applied therapy, and early recognition of acute compartment syndrome are important as they may prevent further damage.

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Hemophagocytic Lymphohistiocytosis in a Critically Ill Adult with Asymptomatic Post-acute COVID-19

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Contents

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Learning Objectives

- Describe the acute clinical presentation of hemophagocytic lymphohistiocytosis (HLH)
- Highlight the importance of tests and imaging for differential diagnosis
- Critical care management and multidisciplinary team involvement

59.1 Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome caused by excessive cytokine release triggered by genetic or acquired dysregulated activation of macrophages, T cells, and natural killer cells [1]. Clinical presentation can include fever, cytopenias, hyperferritinemia, and multi-organ dysfunction which are not specific to this life-threatening condition [2]. Diagnosis can be challenging, as it may overlap or be triggered by other inflammatory states like sepsis or COVID-19 [3, 4]. Mortality rates in adults are high ranging from 75% up to 90% in untreated patients [2]; therefore, early identification and prompt initiation of treatment are critical for improving survival. Currently, the literature reports only a couple of studies of infection-associated hemophagocytic syndrome in critically ill patients with COVID-19 [4, 5]. This report presents a case of a life-threatening HLH occurring 4 weeks after an asymptomatic COVID-19 infection suggesting that HLH can manifest as a post-acute COVID-19 syndrome.

Case Study

Clinical Presentation

A 29-year-old male presented with 10-day history of febrile illness and sore throat. Additionally, he reported 3 days of nausea and vomiting, low volume of red urine, dysuria, and no bowel motion.

His past medical history included uncomplicated rheumatic heart disease. He had no other past medical history and no family history of any positive immune or infective disease. No foreign travel and no weight loss were reported.

Four weeks prior to the current emergency department (ED) visit, the patient was diagnosed with COVID-19, confirmed by PCR via nasopharyngeal swab. At the time, he experienced low grade fever and myalgia with no other symptoms. He self-isolated and his symptoms resolved within 1 week without treatment apart from generic painkillers bought over the counter. No physical examination or laboratory testing was performed at the time. The patient reported no further exposure to COVID-19 prior to this admission.

At the current presentation in ED, he appeared unwell but vital parameters were stable, and he was breathing spontaneously on room air with an adequate blood pressure. He had dry mucus membrane and was visibly jaundice and encephalopathic (grade 1 encephalopathy), complaining of upper abdominal tenderness. The abdomen was generally distended with sluggish bowel sounds, but was not peritonitic with no guarding.

On the initial blood tests, he had raised inflammatory markers, neutrophilia, coagulopathy, hyperferritinaemia, hyponatraemia, mild hyperkalaemia, severe acute kidney injury, and acute liver failure with raised lactate (see Table 59.1).

Table 59.1 Laboratory results from day 0 to day 10 during intensive care admission

Laboratory tests	Day 0	Day 3	Day 7	Day 10
Hemoglobin (g/L)	114	81	85	80
Platelets ($\times 10^9$/L)	101	51	98	248
White cell count ($\times 10^9$/L)	41	46.1	27.2	10.4
Absolute neutrophils ($\times 10^9$/L)	36.2	39.8	24.0	7.7
Absolute lymphocytes ($\times 10^9$/L)	2.1	3.3	1.3	0.9
Absolute monocytes ($\times 10^9$/L)	2.0	2.8	1.8	1.6
INR	2.1	1.4	1.3	1.0
Urea	38.3	20.3	17.4	34.5
Creatinine (μmol/L)	358	303	217	380
Alanine aminotransferase (U/L)	2684	730	329	108
C reactive protein (mg/L)	229	76	28	13
Ferritin (μg/L)	67,812	8618	3750	1389
Lactate (mmol/L)	5.9	1.5	2.0	0.6
Troponin T serum (ng/L)	2468	1117	600	229

An initial chest X-ray was deemed normal with nil acute changes (see Fig. 59.1). He had a CT scan of his abdomen which revealed abnormal ill-defined retroperitoneal soft tissues encasing the coeliac axis and aorta extending into the left common and external iliac and iliac territories, with a small amount of fluid at the tip of the liver, but no lymph nodes (see Fig. 59.2).

A presumed diagnosis of sepsis was made, and treatment with intravenous piperacillin-tazobactam (4.5 g every 8 h) commenced. After initial management with fluid resuscitation, he got worse, i.e., hypotensive, oliguric, and more encephalopathic. He was drowsy with consciousness level dropping by four points on the Glasgow Coma Scale (GCS) (GCS: 11/15) accounting for the following breakdown: E3V2M6. At this point, he was deemed to be in shock with multi-organ failure (cardiac, renal, and liver failure) and was transferred to the ICU for further management and initiation of vasopressor and renal replacement therapy.

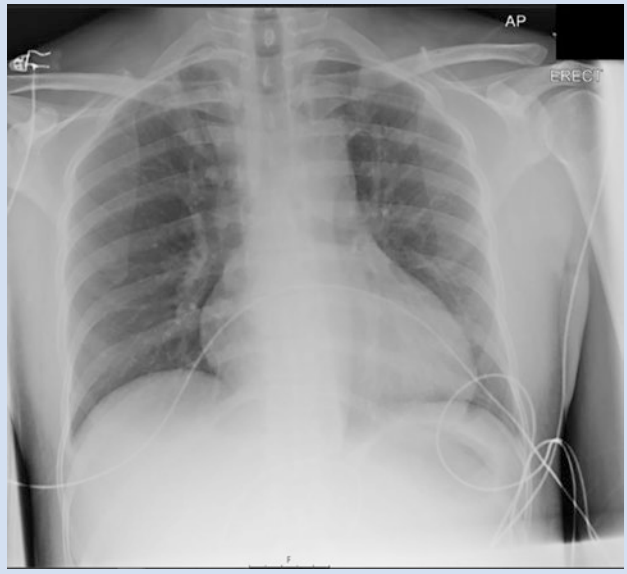

Fig. 59.1 Chest X-ray at day 0

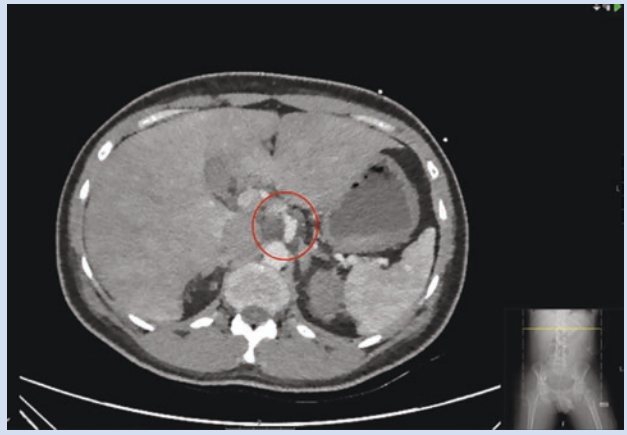

Fig. 59.2 CT-abdomen at day 0 showing abnormal ill-defined retroperitoneal soft tissue

59.2 Investigations

On arrival at the ICU, he had a bedside focused intensive care echocardiogram (FICE) to assess his volume state. The echocardiogram revealed severely impaired left systolic function with an EF of 30–35% by visual estimate, mildly dilated right ventricle with impaired systolic function, and bilateral atria dilatation (i.e., right bigger than the left atria). The myocardium appeared bright, shiny, and wet suggesting a degree of inflammation and volume/pressure load (see Fig. 59.3). Inferior vena

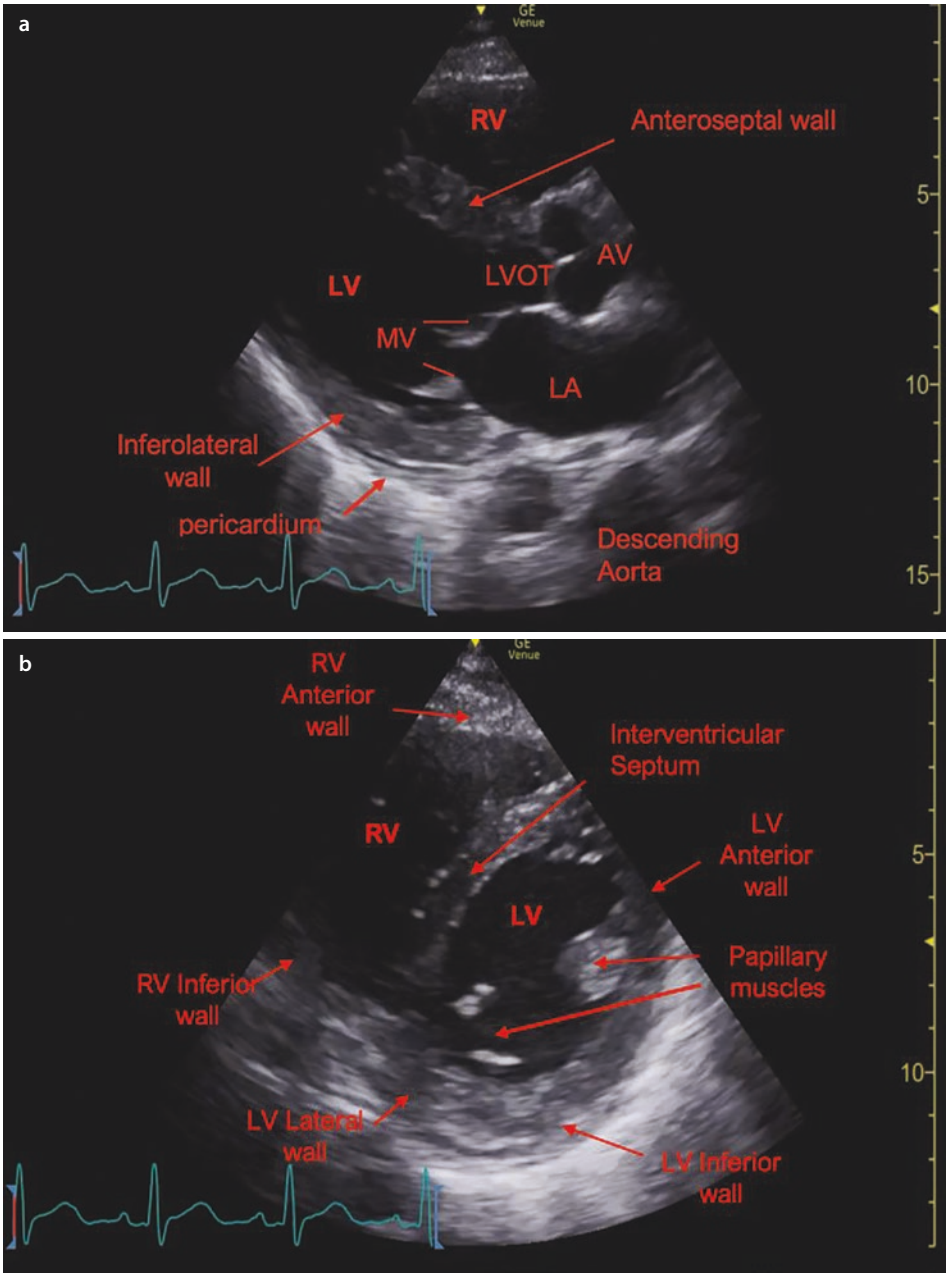

Fig. 59.3 Cardiac views on bedside transthoracic focused echocardiography. (**a**) long parasternal axes view; (**b**) short parasternal axes view. Abbreviations: *RV* Right ventricle, *LV* Left ventricle, *LA* Left atria, *MV* Mitral valve, *LVOT* Left ventricle outflow tract, *AV* Aortic valve

cava (IVC) was dilated and not collapsing on inspiration. Additionally, a focused lung ultrasound showed widespread B-lines and bilateral pleural effusion, in keeping with an overall picture of volume overload.

On day 1, the patient had a CT scan of the neck and chest looking for lymph nodes and additional masses; but nothing was found. On day 2, a formal transthoracic echocardiogram (TTE) confirmed the previous findings and added additional information about valvular issues (moderate to severe tricuspid regurgitation and mild to moderate mitral regurgitation) with signs of pulmonary hypertension. The coagulopathy was corrected with blood product administration guided by rotational thromboelastometry (ROTEM).

Raised ferritin and neutrophilia raised suspicion for HLH, and he had a bone marrow biopsy on day 4 and a liver biopsy at day 7 to exclude autoimmune liver disease. He had multiple bacterial, mycobacterial, and viral cultures and tests for infectious and autoimmune workup, and these all showed no growth or negative results (see ◘ Table 59.2).

Finally, after discharge from the ICU, he had a PET scan (at day 26 of admission) which was normal showing no evidence of underlying malignancy.

◘ **Table 59.2** Infectious and autoimmune workup performed between day 0 and day 15 in intensive care unit

Tests	Results
Aerobic and anaerobic blood cultures ×2	No growth
Urine culture	No growth
BAL culture, *Mycoplasma pneumoniae*	Negative
Legionella, galactomannan, aspergillus antigen	Negative
TB sputum culture	Negative
SARS-CoV-2 PCR x3	Negative
HIV Ab/Ag screen	Not detective
Hepatitis B sAg, hepatitis B sAb, hepatitis B cAb, hepatitis C Ab, Hepatitis E Ab	Not detective
Toxoplasma IgM, IgG, Ig	Not detective
CMV quantitative by PCR	Not detected
Enterovirus PCR blood, adenovirus PCR blood	Negative
Antistreptolysin	Negative
Leptospira	Negative
Parvovirus B19 IgG, IgM	Not detective
Autoimmune serology	Negative
EBV VCA IgM, VCA IgG, EBNA IgG, EBV PCR quantitative	Negative
HTLV-I/II screen ELISA	Negative
Bone marrow tissue biopsy bacterial culture, AFB culture	Negative
Liver tissue biopsy culture	Negative

59.3 Differential Diagnosis

Considering the combination of multi-organ failure, systemic inflammation, and elevated cytokines, the patient seemed to be suffering from a cytokine storm alongside a macrophage activation syndrome (MAS).

Diseases accounting for a cytokine storm picture are manifold and may be overlapping.

The differential diagnoses included bacterial sepsis, viral infection, autoinflammatory disorder, human herpes virus related conditions, secondary HLH, and multisystem inflammatory syndrome associated with SARS-CoV-2.

At the time of decompensation, the patient met three of eight HLH 2004 criteria with a calculated HScore of 163, indicating a 40–54% probability of a hemophagocytic syndrome [6].

The addition of the bone marrow aspirate showing hemophagocytosis increased the patient's HScore to 196 for an 80%–88% probability.

The absence of acute Epstein-Barr virus (EBV), CMV, and HIV infections and the unremarkable autoimmune panel all contributed to the diagnosis.

59.4 Treatment

On arrival at the ICU, we considered the clinical picture, tests, and investigations. It was apparent that the patient was suffering a significant inflammatory response with increased vascular permeability and interstitial leakage but intravascularly depleted. This HLH-septic related picture was causing all the following issues:

- Heart failure with signs of compensated cardiogenic shock
- Acute renal failure, maybe secondary to heart failure and low preload
- Liver failure
- Coagulopathy
- Low level of consciousness, which was multifactorial (hypernatremia, hyperuremia, cytokine storm)

We decided to tackle each problem gradually, and initially we started renal replacement therapy (RRT) for fluid removal and concomitant slow intravenous fluid therapy with dextrose 5% to avoid rapid correction of hyponatremia. Low dose noradrenaline was commenced to improve preload. Intravenous N-acetylcysteine (NAC) infusion was started with 150 mg/kg dose over 1 h and followed by 100 mg/kg of continuous intravenous infusion. The coagulopathy was treated with blood product transfusion (platelets, cryoprecipitate, fresh frozen plasma) guided by ROTEM.

Regarding his low GCS, the initial decision was to "watch and monitor" rather than proceeding with early intubation. Due to the high suspicion for HLH, the patient was treated with a pulsed dose of 1000 mg of methylprednisolone and 100 mg of anakinra (patient weight 65 kg, hence 1.3 mg/kg dose) pending the bone marrow aspirate result.

On day 3, the NAC infusion was stopped, and he hemodynamically improved to the point that noradrenaline was discontinued.

On day 5, he was started on bisoprolol 2.5 mg and amlodipine 5 mg for management of hypertension and preventing further heart failure considering the echocardiography findings.

On day 9, he was established on intermittent renal replacement therapy.

On day 12, he was discharged to the ward for ongoing dialysis via tunneled dialysis line.

Of note, tocilizumab, an anti-IL-6 receptor monoclonal antibody, was not administered in this case of post-acute COVID-19 syndrome since it was thought that tocilizumab would not have blocked the phagocytosis process at the origin of the HLH.

59.5 Evolution, Outcome, and Follow-Up

The patient's clinical picture gradually improved after commencement of methylprednisolone and anakinra. It is important to highlight that he was never intubated, and vasopressor was used only for a brief period on day 2 and day 3 and then stopped. He was successfully established on dialysis via a tunneled dialysis line and discharged to the ward under the joint care of the hematology and renal team.

59.6 Discussion

Since its discovery in 1939, HLH has proven to be a life-threatening condition. Conventionally, HLH is grouped into two distinct categories: primary and secondary. Primary occurs often in children with a genetic predisposition. Secondary occurs more often in adults without a genetic predisposition, but in the context of an immunological trigger (infection, malignancy, etc.) [1, 2]. Both forms are characterized by a dramatic activation of cytotoxic T cells and natural killer cells combined with uncontrolled macrophagic activation leading to a cytokine storm, which can be life-threatening [2]. The incidence of HLH in adults is low, and approximately two-thirds of cases occur in men with a mean age of 50 years. It is unclear whether ethnicity is a predisposing factor [2]. Current guidelines recommend using the HLH 2004 criteria for diagnosis, and treatment with high dose methylprednisolone and anakinra for autoimmune or inflammatory disease induced macrophage activation syndrome (MAS)—HLH [7]. The intensity and duration of treatments are variable depending upon patients' response and clinical picture. Recently, SARS-CoV-2 has also been reported to be associated with secondary HLH with the mortality rate reported to be as high as 54% [4]. The patient described in this case report met the criteria for a post-acute COVID-19 syndrome. However, the interesting aspect is that he suffered from a mild asymptomatic COVID-19 illness 4 weeks prior, and his symptoms self-resolved within 1 week without treatment or hospitalization. Yet he developed a life-threatening immune reaction with severe cardiomyopathy, most likely stressed induced by HLH. The mechanism behind HLH after SARS-CoV-2 infection remains unclear; but it is hypothesized that an aberrant virus-host interaction occurs in the context of elevated cytokines, including IL-6 levels [1, 2]. This case illustrates a delayed and severely modified immune response to SARS-CoV-2 and represents a

new entity of post-acute COVID-19 manifestations. Therefore, a high index of suspicion is necessary for the diagnosis of HLH in patients who have recovered from COVID-19. Bone marrow aspiration and/or biopsy should be carried out promptly to confirm the diagnosis and start appropriate treatments. There currently are no guidelines or algorithm for optimal follow-up of patients who have recovered from COVID-19. Nevertheless, several institutions have already created post-COVID-19 recovery clinics. A follow-up regardless of the severity of initial infection may help to ensure resolution of the prior symptoms and assess for emerging post-acute COVID-19 manifestations.

Take-Home Messages

- COVID-19-associated hemophagocytic lymphohistiocytosis (HLH) can present as a post-acute COVID-19 syndrome, even after a mild asymptomatic initial infection.
- The development of HLH after a SARS-CoV-2 infection is rare and could represent an aberrant virus-host interaction.
- Clinical presentation of HLH includes fever, cytopenia, raised ferritin, and coagulopathy alongside multi-organ failure.
- An initial infection like SARS-CoV-2 can cause a significant inflammatory response leading to cardiomyopathy and cardiogenic shock with low cardiac output state causing acute renal failure and acute liver failure.
- HLH remains a diagnostic challenge since it can mimic severe infections, autoimmune diseases, lymphoproliferative disorders, and multisystem inflammatory syndrome in adults.
- A bedside transthoracic echocardiography and lung ultrasound can support clinical assessment and guide treatment initiation and decision-making management.
- A bone marrow aspirate and/or biopsy should be performed to aid early and definitive and appropriate therapy.
- The optimal duration of immunosuppressive therapy should be made on a case-by-case basis due to the risk of bone marrow suppression and suppurative infection.

Summary

Hemophagocytic lymphohistiocytosis (HLH) causing multi-organ failure is a life-threatening condition, and adult patients often require admission to critical care for organ support therapy. Infections are the most common trigger for HLH, and recognition of HLH patients in the intensive care unit (ICU) is challenged due to the clinical overlap with other infections. This report presents the case of a life-threatening HLH occurring 4 weeks after an asymptomatic COVID-19 infection in a previously healthy adult. The patient was presented with an exaggerated immune reaction, multi-organ failure (i.e., acute kidney injury and acute liver failure), and severe cardiomyopathy, most likely stressed induced by HLH. Organ support included renal replacement therapy and vasopressors and treatment with methylprednisolone and anakinra. Multiple tests and cultures were undertaken to exclude potential coexisting infections, and bone

marrow biopsy was performed to confirm HLH diagnosis. He gradually improved requiring no intubation, and he was discharged to the ward on intermittent dialysis after day 12 of admission to the intensive care unit. To our knowledge, this is one of the first cases of HLH occurring as a post-acute COVID-19 syndrome following an asymptomatic initial infection.

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The Approach to a Patient with a Myasthenic Crisis in an Intensive Care Unit

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Contents

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Learning Objectives

- Diagnosis and differential diagnosis of myasthenia gravis
- Approach to acute respiratory failure in the myasthenic patient
- Anesthetic procedure specificities for the patient with myasthenia gravis
- Treatment of a myasthenic crisis

60.1 Introduction

Myasthenia gravis (MG) is an autoimmune disorder characterized by fatigable skeletal muscle weakness resulting from an antibody-mediated T cell-dependent immunologic attack directed at acetylcholine receptors in the postsynaptic membrane of the neuromuscular junction. The hallmark of MG is a fluctuating degree and variable combination of weakness in the ocular, bulbar, limb, and respiratory muscles. Clinical presentation may be in two forms: ocular and generalized. The symptoms are often transient in an early phase, and new symptoms often develop weeks or months later. The diagnosis is usually established with clinical history and typical examination findings. Preferably, the diagnosis should be confirmed by immunologic and/or electrophysiologic testing.

A myasthenic crisis is a life-threatening exacerbation of MG, compromising respiratory muscles, and severe enough to necessitate intubation. Common precipitating factors include respiratory infections, aspiration, sepsis, surgical procedures, rapid tapering of immune modulation, beginning treatment with corticosteroids, exposure to drugs that may increase myasthenic weakness, and pregnancy [1]. A myasthenic crisis is an indication for admission to the intensive care unit (ICU) and to rapidly initiate treatment with intravenous application of immunoglobulin or even plasma exchange to avoid fatal complications.

Case Presentation

We present the case of a 69-year-old man with a clinical frailty score of 3, with a past medical history of hypertension, dyslipidaemia, and obesity. No relevant epidemiological context or past family history was found.

The patient was presented to the neurology outpatient clinic to assess a 2-month history of new-onset strabismus that fluctuated during the daytime and became more notorious in the late afternoon, accompanied by diplopia and right-side ptosis. A clinical diagnosis of MG was established. Symptoms evolved rapidly within 2 weeks, followed by severe asthenia, cachexia, chewing difficulties, and dysphagia.

The patient was reassessed at the neurology outpatient clinic and was prescribed 60 mg of pyridostigmine four times daily. A slightly favorable clinical evolution was noticed in the first week of treatment. However, after the second week of treatment, the patient evolved with notable upper limb weakness and difficulty walking. The therapy with 40 mg of prednisolone and immunoglobulin 0.4 mg/kg daily was started. Still, his symptoms continued to exacerbate with worsening asthenia, severe dyspnoea at

rest, and inability to complete sentences, which brought him to the emergency department.

Neurological examination at admission revealed preserved superior neurological functions with no field deficits. A right eye in abduction with bilateral eyelid ptosis (more notorious on the right) improved with ice application. The nauseous reflex was preserved. A centred uvula was observed with good palate elevation and tongue protrusion in the midline. Neck flexion deficit and proximal limb deficit aggravated with fatigability.

Although peripheral oxygen saturation was >94%, the patient presented with evident respiratory distress with accessory muscle use. The cardiopulmonary auscultation was normal. No stridor was present.

60.2 Investigations

The initial arterial blood gas panel revealed an acute hypercapnic respiratory failure with pH 7.43, pCO_2 46 mmHg, pO_2 64 mmHg, HCO_3^- 30.5 mmol/L, and SaO_2 94%. Initial laboratory tests showed no leukocytosis with a negative C-reactive protein; hemoglobin, platelet count, and renal and hepatic panels were within normal range. Urine and blood cultures were negative.

The chest computed tomography (CT) scan excluded a thymic expansion and revealed two subpleural nodules (approximately 6.8 mm) and radiological signs suggestive of fibrosis and bilateral emphysema.

Autoantibodies against the acetylcholine receptor (AChR-Ab) and a receptor-associated protein, muscle-specific tyrosine kinase (MuSK-Ab), were requested at admission to confirm the presence of MG. AChR-Ab was elevated >9.0 nmol/L (R: >0.50 positive), confirming a seropositive MG. MuSK-Ab were negative 0.01 nmol/L (R: >0.05 positive).

Thyroid function was assessed with peripheral hormones within range. Antithyroglobulin antibodies were negative 36 UI/mL (R: <40 negative), and antithyroid peroxidase was also negative 14 UI/mL (R: <25 negative). Since serum vitamin B12 level was low at 152 pg/mL (N: 191–663), with no apparent malabsorption stigma nor dietary restrictions, anti-parietal cell antibodies were requested. A positive result of 79.39 U/ml (R: <25 negative) was observed, with the absence of anti-intrinsic factor antibodies 0.8 U/mL (R: <10 negative).

Autoimmune rheumatic disorders are more common in patients with MG compared to age- and sex-matched patients without MG. Recommendations are that antinuclear antibody and rheumatoid factor should be performed if there is a clinical suspicion of a rheumatologic disorder. Our patient had referred to some morning rigidity in the past with unspecified joint pain but with no edema. Antinuclear antibodies, antineutrophil cytoplasmic antibodies, rheumatoid factor, and anti-CCP were negative.

60.3 Differential Diagnosis

We did not find an apparent precipitating factor for the myasthenic crisis. There were no signs of infection, acute-phase reactants were negative, there is no recent suspicious epidemiological contact, and the chest X-ray was unremarkable. The patient denied recent use of drugs that could increase myasthenia's weakness. Therefore, the myasthenic crisis was assumed in the context of a natural evolution of the disease.

This patient presented with a typical course of MG, with a cephalocaudal trend, then evolving into a myasthenic crisis presentation. Other common causes of acute neuromuscular respiratory failure include Guillain-Barré syndrome and amyotrophic lateral sclerosis. Since the patient recently started pyridostigmine, it is essential to recall the possibility of a cholinergic crisis. However, a cholinergic crisis is rarely seen with the dose limitation of pyridostigmine to less than 120 mg every 3 h [2]; therefore, this diagnosis was not presumed as the cause of increasing weakness.

Due to the deficiency of vitamin B12 not associated with anemia, we suspected a type 3 polyglandular syndrome and requested an autoimmune study. Although antiparietal cell antibodies were positive, with a confirmed MG, autoimmune thyroid disease was not confirmed.

The myasthenic crisis is associated with an in-hospital mortality rate of 5–12% [1, 3]. The most common causes of death are multi-organ failure due to sepsis and respiratory failure despite maximal care.

60.4 Treatment

Literature was consulted at ICU admission to review drugs to avoid myasthenia exacerbation (e.g., beta-blockers, magnesium, aminoglycosides, and fluoroquinolones).

The prednisolone dose was increased to 1 mg/kg/day, and the patient continued pyridostigmine 60 mg four times a day and completed the intravenous immune globulin (IVIG) scheme with 0.4 g/kg. Due to increased respiratory distress and aggravating respiratory alkalosis (blood gas analysis evolution from pH 7.41, pCO_2 46 mmHg, pO_2 64 mmHg, HCO_3^- 30.5 mmol/L, and lactate 0.7 mmol/L to pH 7.49, pCO_2 15 mmHg, pO_2 126 mmHg, HCO_3^- 25.7 mmol/L, and lactate 1,9 mmol/L), with poor response to noninvasive ventilation (NIV), we decided to perform awake orotracheal intubation with rapid sequence induction, using propofol and remifentanil. Low-dose rocuronium was necessary for muscle relaxation for intubation, knowing we could have an immediate reversal with sugammadex available if required. The strategy for this patient was to maintain the lowest effective dosage for an "awake ICU" strategy for a Richmond Agitation-Sedation target of 0 to −1.

Given the condition of respiratory difficulty in progression, requiring invasive ventilation, and the expected late response to treatment with immunoglobulin, we decided to start plasma exchange.

Our treatment approach was thoroughly discussed with the neurology and nephrology department. In total, the patient was submitted to seven therapeutic plasma exchanges over 14 days, initially on alternative days, followed by every other day. Fluid albumin replacement was done accordingly.

60.5 Evolution, Outcome, and Follow-Up

The patient had an excellent response to the plasma exchange. A physical rehabilitation protocol was tailored and initiated on the first day of the ICU stay. Weaning of invasive medical ventilation started early, and the patient was extubated 48 hours later. After extubation, NIV in bi-level positive airway pressure mode was started. The patient tolerated the NIV with no post-extubation respiratory failure, and we decided to intercalate with high-flow nasal cannula for patient comfort.

A nasal pharyngoscopy was performed 24 h after extubation to evaluate the safety of initiating an oral diet. Due to slight edema of the arytenoids, with reduced glottic lumen due to hypomobility of the vocal cords, we maintained the nasogastric tube (initially introduced at admission due to the severe dysphagia) for a few more days until further resolution of the myasthenic crisis.

The rehabilitation specialists also played a crucial part in the patient's recovery with early respiratory physiotherapy, using a mechanical in-exsufflation device to guarantee bronchial airway hygiene with secretion mobilization. The speech therapist also addressed the patient.

Once the cycles of plasma exchange were completed, with the stabilization of the patient, he was transferred to the neurology department ward, and rituximab therapy was started. An otolaryngologist again evaluated him with the guarantee of a safe airway to initiate an oral diet. The patient was discharged 15 days after hospital admission, with a normal neurological examination, walking on his own feet with no support and no asthenia.

The most common complications associated with the myasthenic crisis are various causes of fever and infection. Our patient had a nosocomial urinary tract infection during the ICU stay with a penicillin-susceptible strain of *Enterococcus faecalis* isolated in a urine culture. He completed a 7-day course of ampicillin according to the antibiogram.

Follow-up was initially done in the neurology day hospital, with a favorable evolution. He continued to work with rehabilitation specialists for respiratory rehabilitation and general physiotherapy for muscle strengthening.

The patient was referred to a pulmonology consultation for a follow-up of the two subpleural nodules found on the initial CT scan for radiological follow-up.

60.6 Discussion

We describe a clinical case of a patient with a myasthenic crisis with respiratory failure—a clear indication for admission to an ICU. In a myasthenic crisis, the initial use of NIV to avoid intubation must be individualized [3]. However, it should not delay invasive mechanical ventilation, with a low threshold for elective intubation. In the post-extubation period, poor cough strength is associated with significant in-hospital morbidity in these patients. Respiratory physiotherapy is essential, and there may be benefits to using NIV in this period to prevent extubation failure [3].

Plasma exchange and IVIG are the recommended rescue therapy for myasthenic crisis as they have a rapid onset, usually over days, and can be used as bridge therapy [4]. We decided on plasma exchange, as the expert consensus suggests that plasma

exchange is more effective and works more quickly [4]. IVIG was continued as he had begun treatment with IVIG recently. We decided to begin glucocorticoid to provide a more extended benefit period, and rituximab was started before the patient's discharge as immunomodulatory therapy for refractory generalized MG.

The anesthesia management in patients with MG is complex. Generally, ultrashort- or short-acting anesthetic agents are preferred, and neuromuscular blocking agents (NMBA) should be avoided. In anesthesia induction, propofol is most used due to its short duration and rapid onset. It can be used in combination, preferably with remifentanil, since it is an ultrashort-acting opioid. If necessary, nondepolarizing NMBA can be used, such as rocuronium or vecuronium, as patients with MG are resistant to depolarizing NMBAs. Patients with MG are highly sensitive to low doses of nondepolarizing NMBAs, and their use is not advised if sugammadex is unavailable.

A myasthenic crisis can be precipitated by concurrent infection, surgery, pregnancy, childbirth, certain medications, tapering of immunotherapeutic drugs, or spontaneously as part of the natural history of the disease. After excluding the several triggers, the myasthenic crisis in our patient was assumed in the context of a natural evolution of the disease.

AChR-Ab has a high sensitivity for generalized MG of 80–90% [5]. Our patient had positive AChR-Ab, providing the laboratory confirmation of MG. In our case, MuSK-Ab were unnecessarily requested and usually only requested if AChR-Ab are negative, with high clinical suspicion. MG can also be considered a paraneoplastic effect of thymoma but rarely of extrathymic tumors. With the confirmation of MG, a chest CT scan was done to exclude thymic abnormalities. Nonetheless, MG has been associated with small cell lung cancer and Hodgkin lymphoma. Therefore, it was essential to follow up on the subpleural nodules found on the initial CT scan.

Take-Home Messages

- Myasthenia gravis is a rare autoimmune condition characterized by fluctuating weakness involving the ocular, bulbar, limb, and/or respiratory muscles. The severity of symptoms ranges from ocular muscle palsy to generalized muscular weakness with neuromuscular respiratory fatigue.
- Myasthenic crisis is a life-threatening exacerbation of myasthenia gravis that is defined as worsening of myasthenic weakness requiring intubation or NIV frequently accompanied by severe bulbar muscle weakness. NIV should not postpone orotracheal intubation.
- Careful use of anesthetic drugs is recommended during induction. Ultrashort- or short-acting anesthetic agents are preferred, and NMBAs should be avoided.
- Treatment for MG may be symptomatic with pyridostigmine or immunosuppressant. When a myasthenic crisis installs, rapid onset treatment must be initiated, with plasmapheresis having the quickest time to onset of 1–7 days.

Summary

MG is an autoimmune disorder characterized by fatigable skeletal muscle weakness resulting from an antibody-mediated reaction against acetylcholine receptors in the postsynaptic membrane of the neuromuscular junction. A myasthenic crisis is an MG exacerbation that may require ventilatory support.

We present the case of a 69-year-old man recently observed in the outpatient clinic due to ocular manifestations of MG. He was started on pyridostigmine but evolved with out-of-proportion muscle weakness when chewing and later difficulty walking due to extreme weakness. He presented to the emergency room with respiratory failure and was admitted to the intensive care unit to rapidly initiate plasma exchange, high-dose glucocorticoid, and intravenous immune globulin. Initially, we attempted noninvasive ventilation, but orotracheal intubation was necessary. Induction of anesthesia was done with a caution of choice of drugs, preferably with ultrashort- and short-acting agents, and avoiding using neuromuscular blocking agents.

The patient responded well to plasma exchange and was extubated in 48 hours. After extubation, noninvasive ventilation was initiated. The rehabilitation team was crucial for the patient's recovery. Rituximab was started, and the patient was discharged 15 days after hospital admission, with a normal neurological examination, walking on his own feet with no support and no asthenia.

No precipitation factor was identified; therefore, the myasthenic crisis was assumed to be part of the natural history of MG. In our diagnostic workup, the patient also presented with pernicious anemia that raised suspicion of type 3 autoimmune polyglandular syndrome. However, thyroid function was normal, and no thyroid antibodies were found.

The case report highlights the importance of initiating treatment early, with a lower threshold for orotracheal intubation in patients with respiratory failure. Precautions must be considered when treating a patient with MG, especially when considering which drugs to administer.

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A Usual Presentation of an Unusual Case

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Contents

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Learning Objectives

- Learn to list differential diagnosis of fever of unknown origin.
- Learn about a rare but life-threatening rheumatologic condition.
- Learn about the investigations and treatment of AOSD complications.

61.1 Introduction

High grade fever with elevated white cell count and CRP is a very common presentation to the ICU, either on admission or during the ICU stay, triggering a search for infective causes. However, there are not many rheumatologic diseases in which immune reaction can quickly spiral out of control when the diagnosis is not made in timely manner. The aim of this case presentation is to remind readers about adult-onset Still's disease (AOSD) which is estimated to affect 0.16:100.000 adults and its complication of monocyte activation syndrome (MAS) also known as hemophagocytic lymphohistiocytosis (HLH).

The most common presentation of AOSD includes remittent fever >39 °C, salmon-colored skin rash, joint involvement, and leukocytosis. Still's disease in adults has significant mortality and morbidity, and serious complication affects 15% of patients and can include ARDS, liver failure, renal failure, MAS/HLH, and disseminated intravascular coagulation (DIC).

Usually, treatment involves induction dose of steroids followed by immunosuppression therapy, which might be challenging to be introduced until full septic workup is completed.

Case Presentation

A 32-year-old male with a background of ulcer disease and no other relevant past medical history was admitted to the emergency department (ED) with acute upper quadrant abdominal pain and fever up to 38 °C. Two days before ED admission, the patient experienced sinusitis and cough.

On initial examination, he looked distressed, mildly tachycardic (110/min), and hypotensive (BP 100/60) with a temperature of 39 °C. The abdomen was not distended with muscular guarding on examination and pain of 8/10 on numeric rating scale (NRS). He was admitted under the care of the surgical team as a perforated ulcer was suspected despite the initial plain abdominal X-ray being unremarkable. Initial blood tests revealed WBC 23 10^9/L, neutrophils 19.6 10^9/L, Hb 12 g/dL, CRP 235 mg/dL, NT-proBNP 2580 pg/mL, and troponin I 1.97 ng/mL (< 0.06). The subsequent CT abdomen identified no gastrointestinal (GI) pathologies. Acute surgical abdomen was ruled out in the ED and patient was admitted to general medical ward.

61.2 Investigations

Sepsis and malignance were suspected in the first instance, and extensive workup was done including serial lab test as shown in Table 61.1 and Fig. 61.1. Note that there was an initial increase in inflammatory markers followed by marginal decline and then a second episode of massive inflammation manifested by high CRP, high ferritin, and DIC-like coagulation derangement. Microbiological workup was done in the form of virology screening for SARS-CoV-2, CMV, EBV, HIV, HCV, HBV, and influenza A/B which were all initially negative. Parvovirus B-19 was positive initially. Serial blood culture, pleural effusion culture, toxoplasmosis, chlamydia, *Campylobacter*, *Yersinia*, *M. tuberculosis*, and *Treponema pallidum* were all negative as well. Multimodal imaging approach was followed to elicit a source of infection or possible malignancy; echocardiography showed pericardial effusion with no other abnormalities, ultrasound scanning of the abdomen and pelvis showed hepatosplenomegaly and trace of free fluid in the pelvis, and the liver elastography and flow patterns were normal. CT scan of the chest, abdomen, and pelvis were not conclusive for source of infection showing bilateral pleural effusion. PET-CT scan with 18F-FDG showed increased signal from lymph nodes in the neck, thorax, and spleen suggestive of lymphoproliferative disease. Gastroscopy was normal. Autoantibody screen was negative for RF, ANA, and ANCA. Bone marrow biopsy revealed decreased CD34(+) and CD117(+)—hypoplasia might suggest infection of parvovirus B19 and a possible post infective bone marrow defect. There are no leukemia or MDS features.

Table 61.1 Lab results

LOS [day]	0	3	5	10	14	17	18	22	25	27	34
WBC [10^9/L]	23	17.6	14.5	23.6	21	10.2	13.7	31.3	12.04	8.5	2.29
PLT [10^9/L]	208	301	338	539	496	250	171	39	115	160	202
Hb [gm/dL]	12.6	11	9.6	9	9.5	10	10.7	9.4	8.5	9.2	9.3
CRP [mg/L]	235	297	247	248	145	75	76	32	9	77	54
PCT [ng/mL]		0.6	0.27		0.51			2.32	0.51		0.12
Ferritin [ng/mL]			1014				76,032	24,123	6350	3940	3715
ALT [U/L]	59	32			26			672	349	238	249
AST [U/L]	40	19			21			184	58	43	64
LDH [U/L]					185			466	224	209	
INR	1.3		1.68		1.76	1.75		1.06	1.02	1.09	1.07
D-dimer [ng/mL]	1362		2884		5472	>10.000	>10.000				
Fibrinogen [mg/dL]	909		760		528		280	136	149	427	843
Triglyceride [mg/dL]		108						414	299		
Troponin-I [ng/mL]	1.973	0.985	0.64	0.221	0.018	0.03					

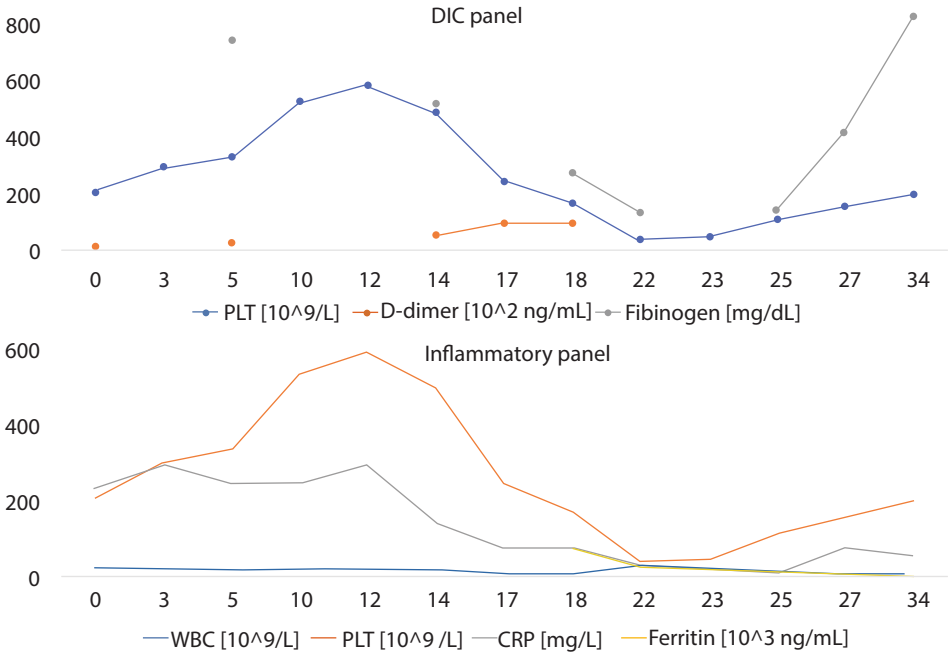

Fig. 61.1 DIC and inflammatory lab panel

61.3 Differential Diagnosis

Given the nonspecific presentation of our case, a long list of differential diagnosis was proposed, and extensive workup was required as mentioned above, and sepsis was suspected initially, but the absence of a clear source, the negative results of the microbiological tests, and the failure of therapeutic trial of broad spectrum antibiotic course made sepsis less likely. Viral and atypical infections were excluded as well. Malignance was also included in differential diagnosis, and solid organ malignancies were excluded based on both imaging and biochemical investigations. The initial full blood count, blood film, and bone marrow biopsy didn't show any evidence of hematological malignancy. The presence of rash and fever raised the suspicion of rheumatologic disease; accordingly, autoantibody screen excluded the seropositive group of rheumatologic disease. AOSD was suspected, and a decision was made to start steroid therapy (no induction dose) after exclusion of other reasons of the presentation of the case and after the exclusion of any active infection.

61.4 Treatment

Antipyretic treatment: paracetamol 4 g a day, metamizole 4 g a day, and ketoprofen 150 mg a day. Antimicrobial therapy: escalated to broad spectrum antibiotics and antifungals. Immunomodulation: 62.5 mg of solumedrol was started on day 18 and followed by 3-day course of IV immunoglobulins 0.5 g/kg/day at day 25.

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61.5 Evolution, Outcome, and Follow-up

During the first week, initial septic screen was performed, and the patient was started on trial of different empiric broad spectrum antibiotics (vancomycin, meropenem, clindamycin, doxycycline) for potential chest infection and plausible infective endocarditis. Troponins and BNP were downtrending, and repeated echocardiography did not reveal systolic or diastolic dysfunction, valvular pathologies, or wall motion abnormalities. Subsequent chest and abdomen CT showed hepatosplenomegaly, small bilateral pleural effusion, and atelectasis. Pleurocentesis was performed and the analysis revealed an inflammatory exudate.

The patient had daily spikes of fever up to 40 °C despite multiple antipyretic agents. Arthralgia appeared mostly in the left shoulder joint; the pain was described as being localized, sharp, and 10/10 on NRS score. X-ray and ultrasound did not reveal any gross joint abnormalities.

Two weeks after the admission, the patient remained stable from both respiratory and cardiovascular perspective with a preserved renal function. The main symptoms remained debilitating fever up to 40 °C, transient arthralgia, and allodynia of the whole body. Inflammatory markers remained elevated with WBC >20 × 10^9/L and CRP >200 mg/dL, and PCT remained unremarkable. In search of infection source or malignancy, PET-CT, gastroscopy, and bone marrow biopsy were performed.

On day 17 after admission, the general condition of the patient deteriorated, and the patient required oxygen supplementation, and there was a very dynamic change in lab values (Table 61.1). Both WBC and platelet counts dropped, D-dimer rose, and fibrinogen dropped. The computed tomography pulmonary angiogram was performed and excluded pulmonary embolism.

A new rash appeared on both feet (Fig. 61.2), and the decision was made to start empirically low dose steroids as no unifying diagnosis was reached at that point, but Still's disease was suspected as a diagnosis of exclusion. After one dose of steroids, the patient improved remarkably and was able to walk around the unit for the first time in days. However, the clinical improvement was not sustained, and after only a day, the patient continued to deteriorate requiring oxygen supplementation and becoming hypotensive. At this time, diagnosis of hemophagocytic lymphohistiocytosis (HLH) was suspected based on 96% on H-Score, fever, hepatosplenomegaly, cytopenia, markedly elevated ferritin, hypertriglyceridemia, and hypofibrinogenaemia (Table 61.1). The therapy with immunoglobulins was started which led to gradual clinical, morphological, and biochemical improvement.

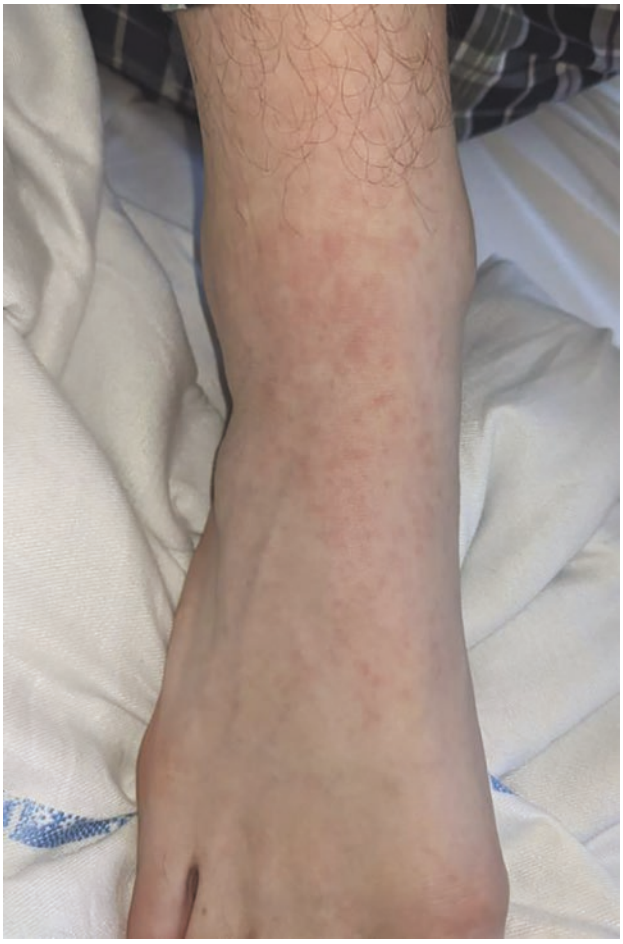

Fig. 61.2 Foot rash

61.6 Discussion

AOSD is a rare multisystem inflammatory disease characterized by spiking high fevers, arthritis or arthralgia, maculopapular salmon-colored rash, neutrophilic leukocytosis, and hyperferritinemia. Owing to an increased awareness about AOSD, incidence and prevalence rates have increased over time [1].Since the nonspecific clinical features of AOSD may pose a diagnostic challenge, several criteria have been developed for the identification of AOSD patients. The Yamaguchi classification criteria are the most widely used criteria for AOSD (Table 61.2) [1]. The initial presentation of the patient was predominantly abdominal pain which is not unusual for AOSD. Hori and colleagues have described a case with a presentation of acute intestinal pseudo-obstruction as a complication of AOSD [2]. Similar case was presented by Gopalarathinam and colleagues when the patient was initially treated for infection and underwent extensive workup for infective and hematological conditions [3].

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Table 61.2 The Yamaguchi criteria for AOST

The Major Yamaguchi
Fever >39 °C lasting > 1 week
Arthralgia > 2 weeks
Skin rash that is salmon-colored in appearance and usually found over the trunk or extremities during febrile episodes
Leukocytosis >10,000/microL
The Minor Yamaguchi
Sore throat
Lymphadenopathy
Hepatomegaly or splenomegaly
Abnormal liver function tests
Negative ANA and rheumatoid factor

However, in our case, the clinical course was more dynamic and involved also complications of uncontrolled cytokine storm which is referred as monocyte activation syndrome (MAS) also known as hemophagocytic lymphohistiocytosis (HLH) and affects 12% of patients with AOSD.

Secondary HLH is usually attributed to conditions undermining immune system. Viral infections (such parvovirus B19, EBV, CMV, HSV, HIV, HBV or HCV) are common causative factors. Parvovirus B19 infection may present similarly to AOSD. The recurrent symptoms of our patients requiring long-term methotrexate and steroids favor AOSD triggered by viral infection rather than manifestation of parvovirus B19 infection. Other conditions leading to acquired HLH include malignancies (mainly hematological neoplasms, especially lymphoma), autoimmune diseases (such as systemic lupus erythematous, adult-onset Still's disease, and rheumatoid arthritis), and also recently after immunization [4].

In HLH, there is a loss of regulation within the immune system leading to inappropriate activity of macrophages and T-cells and a state of uncontrolled, self-perpetuating hyperinflammation. This "cytokine storm" is characterized by unregulated release of tumour necrosis factor-α (TNF-α), IFN-γ, IL-6, IL-10, and IL-1B and marked decrease in natural killer cell activity [5]. HLH causes a constellation of nonspecific findings, including persistent fever, altered mental state, rash, cytopenias affecting all cell lines (often with thrombocytopenia initially), elevated lactate dehydrogenase (LDH), hepatosplenomegaly, lymphadenopathy, and transaminitis. Typically, patients have hyperferritinemia (highly elevated ferritin >10,000 μg/L may be suggestive of HLH in some contexts) with elevated triglycerides and decreased fibrinogen. However, often one or more of these abnormalities are not seen [6].The H-Score developed by Fardet et al. is the first diagnostic scoring system for secondary HLH to be validated in adults [6]. A high index of suspicion in patients with symptoms of unexplained SIRS, multi-organ dysfunction syndrome, and laboratory abnormalities is essential to reduce mortality.

Take-Home Messages

- It is not always sepsis only.
- Rheumatologic diseases present sometimes nonspecific features and need high degree of suspicion.
- Multidisciplinary team discussion and involvement is pivotal in the ICU practice.

Summary

AOSD is characterized by the classic triad of persistent high spiking fever, arthralgia, and salmon-colored skin rash. There is no specific test for diagnosis of AOSD, but classification criteria are available. Timely diagnosis and treatment of the disease with corticosteroids followed by maintenance therapy with disease modifying antirheumatic drugs (DMARDs) or biologic drugs such as TNF-α agents or interleukin (IL-1) antagonists can prevent complications and lead to a favorable prognosis. Management of AOSD comprises of several challenges, including difficulty in diagnosis and need for aggressive immunosuppressive treatment which might be detrimental when misdiagnosed. Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of uncontrolled, severe systemic inflammation (hyperinflammation) which can be triggered as a complication of many systemic diseases including AOSD.

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Correction to: Best 2022 Clinical Cases in Intensive Care Medicine

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Correction to:
Chapter 17 and 55 in: D. Pérez-Torres et al. (eds.), *Best 2022 Clinical Cases in Intensive Care Medicine*, Lessons from the ICU, https://doi.org/10.1007/978-3-031-36398-6

The original versions of chapters 17 and 55 of this book were inadvertently published with incorrect authorship. An author's name has been included after publication. The authorship has been updated with this correction to read as follows:

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