EDTNA/ERCA
Caring Together

Managing Renal Support

in times of **War** and **Mass Disasters**

Editors
Chrysanthi Avrami
Ioannis Stefanidis

First edition: October 2023

European Dialysis and Transplant Nurses Association/ European Renal Care Association (EDTNA/ERCA)

Seestrasse 91, CH 6052 Hergiswil, Switzerland
www.edtnaerca.org

ISBN: 978-618-86506-9-5

Layout, Binding and Printing:
RAT Advertising LTD
156 I. Gkoura Str
PO: 18452 - Athens, Greece
www.rat.gr

EDTNA/ERCA
Caring Together

Managing Renal Support in times of War and Mass Disasters

Editors

Chrysanthi Avrami, RN, Msc, PhD(c)
Senior Renal Specialist Nurse,
Health Core Training Military School,
Athens, Greece
EDTNA/ERCA CKD Consultant

Ioannis Stefanidis, MD, PhD, Professor,
Department of Medicine, University of Thessalia,
Larissa, Greece

Authors

Ioannis Stefanidis, *MD, PhD, Professor,*
Department of Medicine, University of Thessalia,
Larissa, Greece

Chrysanthi Avrami, *RN, Msc, PhD(c)*
Senior Renal Specialist Nurse,
Health Core Training Military School,
Athens, Greece
EDTNA/ERCA CKD Consultant

Reviewers

Jane Golland, *RN, MA*
EDTNA/ERCA Treasurer and Executive Committee Member

Chava Kurtz, *RN, MA, PhD(c)*
EDTNA/ERCA RenalPro Moderator

English Proofreading

Claire Carswell, *RMN, PhD*
Post-Doctoral Research Fellow,
School of Nursing and Midwifery,
Queen's University Belfast, UK.
EDTNA/ERCA Scientific Board Member

Acknowledgements

This is an initiative of EDTNA/ERCA with the aim of producing a book with up-to-date information on *Managing Renal Support in times of War and Mass Disasters* for renal nurses and other healthcare professionals.

EDTNA/ERCA would like to thank the editors for their time and effort in writing their chapters out of a commitment to supporting education of healthcare professionals. The valuable input received from the reviewers from the EDTNA/ERCA Scientific Board is greatly appreciated.

Foreword by
Anastasia Liossatou, *RN, Dip (Edu), MSc, PhD(c)*
EDTNA/ERCA Executive Committee Member
Publications Coordinator
Head Nurse, Dialysis Unit, The General Hospital of Kefalonia, Argostoli, Kefalonia

Sponsor

EDTNA/ERCA would like to thank Fresenius Medical Care for sponsoring the development of the PDF and the printing of the English version of this book.

Table of Contents

Foreword

Mass disasters and wars have a devastating effect on the lives of all afflicted people by destroying infrastructure and obstructing access to life-saving treatments. Insufficient quality of care raises the risk of morbidity and mortality for patients whether they remain in affected regions or are relocated. The majority of healthcare professionals in Europe have limited experience in dealing with the specific demands and complexities that arise from war or large-scale disasters. Providing optimal care for patients with acute or chronic kidney disease requires an enhanced level of focus as the patients' chances of survival depends on access to advanced equipment and highly skilled healthcare professionals.

In recent years, there has been a growing focus on the impact of war or disasters on the delivery of dialysis services. This has emphasised the significance of establishing and implementing structured management procedures within dialysis facilities. Catastrophic events can arise from various sources, including natural occurrences like earthquakes, tsunamis, typhoons, storms, and floods, as well as epidemics such as the recent COVID-19 pandemic. Additionally, they can be caused by human activities or anthropogenic causes, such as fire, terrorist acts, chemical or nuclear hazards, explosives, or even warfare.

Managing renal support in times of war and mass disasters entails navigating demanding situations that increase the prospect of health-related complications and logistical difficulties. People with chronic kidney disease (CKD) need ongoing nutritional support and pharmacologic treatment, and for those patients who are on haemodialysis (HD), a significant amount of energy, water and basic infrastructure are required. Likewise, a wide variety of therapeutic and auxiliary devices and a continual supply of materials are required for performing peritoneal dialysis (PD). Transplant recipients require immunosuppressants to prevent rejection. Disasters can impede the delivery of dialysis treatment, thereby causing detrimental effects on patients. These adverse outcomes may encompass missed HD sessions, heightened rates of hospital admissions, and aggravation of co-occurring medical conditions such as diabetes, hypertension, and cardiovascular disorders. Furthermore, individuals receiving HD treatment may be vulnerable to developing post-traumatic stress disorder as a result of factors such as being required to relocate, prolonged separation from family and friends, and a lack of social and emotional support.

This book provides insights into renal management strategies in various types of mass disasters and war situations. The approaches to managing these circumstances are dependent upon several factors, including the nature of the disaster, the geographical location, the ability to anticipate the event, the potential consequences based on regional environmental assessments, and the prevailing political and social conditions specific to each area.

Ensuring adequate preparedness of dialysis units is a crucial aspect of disaster management in nephrology healthcare. Insufficient emergency planning may result in a situation in which the healthcare facility and its staff are well-equipped to cope with the challenges of providing care during an emergency

Anastasia Liossatou
EDTNA/ERCA Executive Committee Member
Publications Coordinator

Chapter 1

Managing Acute Kidney Injury in mass disasters during peace

Learning objectives

- To define disasters in terms of lack of access to dialysis care
- To increase renal nurses' knowledge of the causes of crush syndrome and its treatment
- To raise awareness of the importance of establishing appropriate protocols in renal units
- To describe the purpose of the Renal Disaster Relief Task Force

Introduction

Disasters can pose a significant risk to individuals with kidney failure as they may be unable to access necessary dialysis care.[1] In times of peace, such events may include earthquakes, typhoons, and epidemics.

One such example of a large-scale natural disaster is an earthquake.[2] Daily occurrences of earthquakes with a magnitude of 4.0 or higher on the Richter scale occur daily worldwide. The unpredictability of earthquakes often results in large numbers of deaths and health-related issues due to building collapses.[3] The main factors that contribute to the severity of impact are poor quality of buildings, dense population in high-risk areas, and the absence of efficient rescue systems capable of addressing renal complications in these situations.[4]

The incidence of earthquakes leading to a need for kidney support, specifically for crush syndrome, are steadily increasing. Crush syndrome refers to the systemic effects of muscle crush injury following direct trauma or ischemia reperfusion injury.[5] A country that experiences frequent earthquakes is Japan. As a consequence, the country places emphasis on school disaster education for over 30 years, as it enhances knowledge and awareness and therefore improves the response to earthquake disasters.[6]

In the aftermath of a large earthquake, nephrology professionals play a significant role not only in the prevention and treatment of acute kidney injury (AKI) and hyperkalaemia (both consequences of crush syndrome) but also in the restoration of renal facilities and services.[3]

Crush syndrome

Crush syndrome is a significant cause of death, ranking second most common form of death from direct trauma, among survivors of earthquakes, regardless of whether acute kidney disease occurs or not.[7] The term "crush syndrome" was first introduced in 1941 during the aerial bombardment of London when survivors were rescued from collapsed buildings.[8]

According to Sever & Vanholder,[7] crush syndrome is defined as the combination of crush injury and systemic manifestations resulting from muscle damage. These systemic manifestations may include acute kidney injury (AKI), sepsis, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), bleeding, hypovolaemic shock, cardiac failure, arrhythmias, electrolyte imbalances, and psychological trauma.[7]

The incidence of crush syndrome after major earthquakes has been estimated to be least 2-5%. Nearly 50% of patients with crush syndrome develop acute kidney injury, and almost half of these cases will require dialysis therapy. Additionally, the mortality rate for rhabdomyolysis resulting in acute kidney disease has been estimated to be 40%.[9]

Renal Disaster Relief Task Force (RDRTF)

The RDRTF was established in 1989 following a significant earthquake in Armenia. It operates under the International Society of Nephrology (ISN) and offers nephrological care support in mass disasters when there is an increased demand for dialysis therapy due to conditions like rhabdomyolysis and crush syndrome. The team consists of nephrology nurses, nephrologists and technicians who work to restore the functional ability of dialysis machines and water treatment systems.[10]

When the decision is made to intervene, the RDRTF follows a planned course of action outlined in a flow chart. This chart, shown as Figure 1, provides guidance for the RDRTF's response based on a specific case, such as the intervention during the 1999 Marmara earthquake in Turkey.[10]

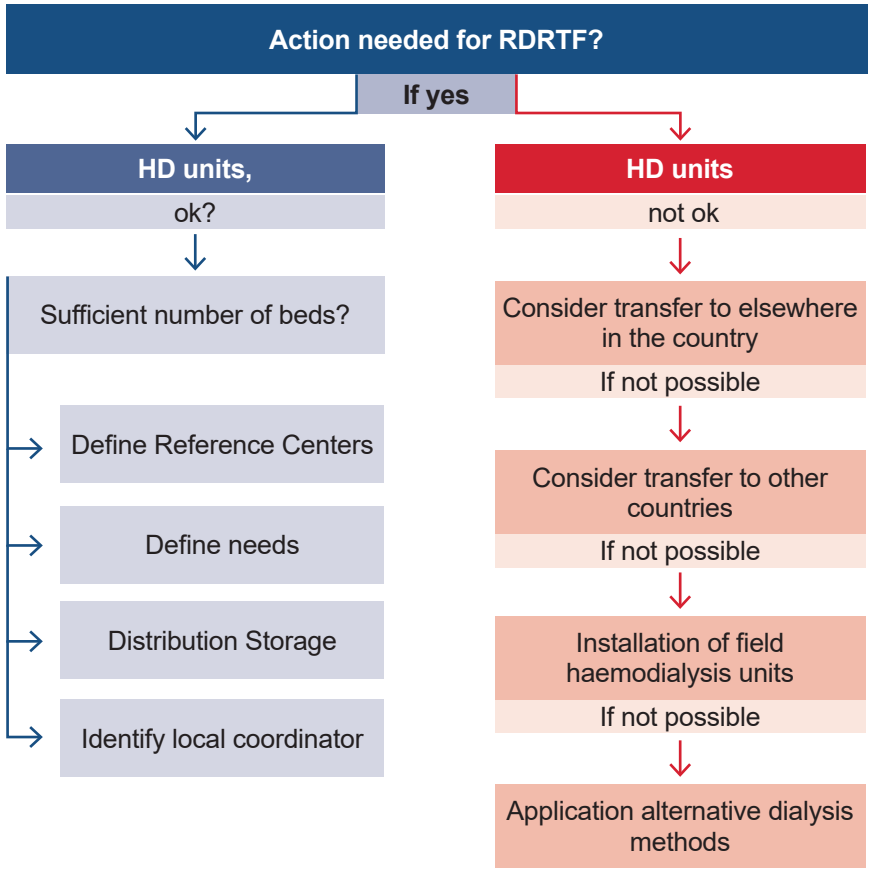


***Figure 1**.Chart of planned course of action of RDRTF.*

In the event of an earthquake, 40% of severely injured individuals will die within the first 6 hours, while 60% of deaths occur within the first 24 hours. The remaining deaths occur within the subsequent 72-hour period. If rescue teams are able to reach the affected areas within the first 3 hours, they have the potential to save 90% of survivors. However, if the rescue efforts are delayed by 6 hours, the percentage of survivors decreases to 50%. As time passes, the chances of successful rescue diminish, and after a period of 10 days, attempts at rescue become futile.[11]

Summary of recommendation statements Intervention before extrication

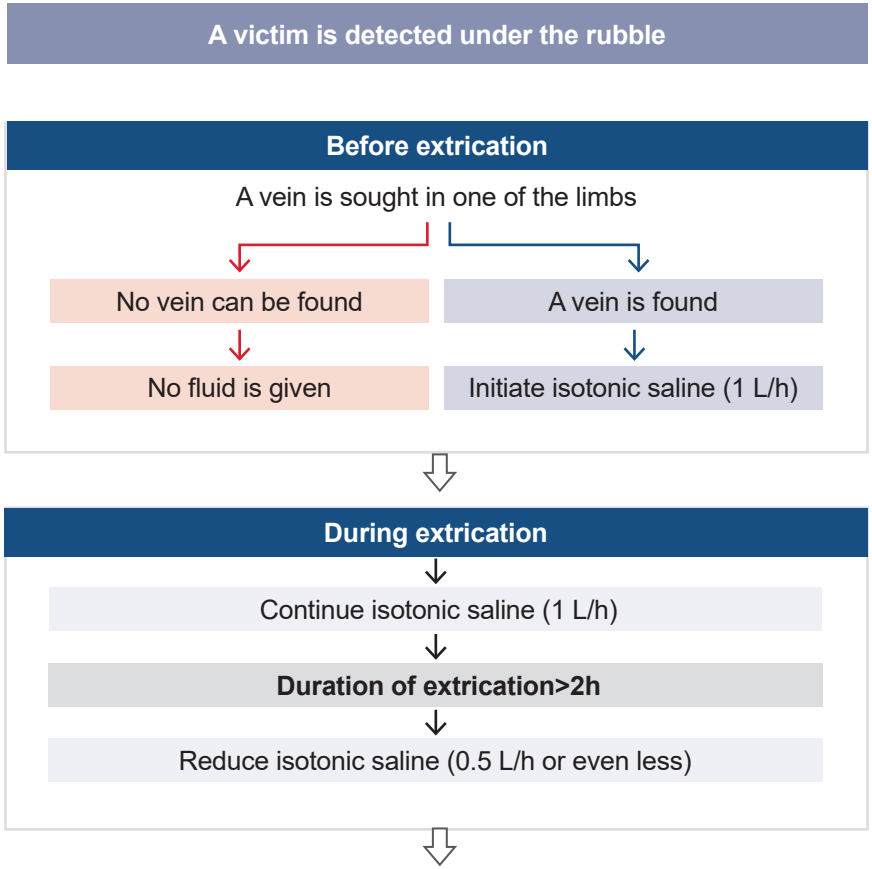
Mass disasters cause chaotic conditions. Staff in medical facilities may have to work continuously without rest, while facing challenges such as lack of communication, electricity, and water. In such situations it is essential for medical personnel to be trained to follow a specific protocol to effectively respond to the crisis. According to Sever & Vanholder,[7] the following steps are recommended:

1. Ensure personal safety: Prioritize the safety of the medical staff themselves to avoid further harm or injury.
2. Educate rescuers on vital interventions: Rescuers should be knowledgeable about essential interventions for individuals trapped in the disaster, particularly those related to crush injuries, fluid resuscitation, and crush-related acute kidney injury.
3. Conduct medical evaluation: Once communication is established with an entrapped victim, perform a thorough medical evaluation to assess their conditions and needs.
4. Establish venous access: Place venous access in any available limb, even if the victim still trapped under rubble. Use isotonic saline solution and avoid solutions containing potassium, such as Ringer's lactate. If peripheral venous access is not possible, consider intra-osseous infusion. In cases where neither intra-osseus infusion nor peripheral venous access is feasible, hypodermoclysis (subcutaneous infusion) may be considered as an alternative.

Following these protocols can help medical staff prioritise their own safety, provide essential interventions, and ensure proper medical evaluation and treatment for entrapped victims in mass disaster situations.

Intervention during extrication

The duration of extricating entrapped victims may vary from 45 minutes to 8 hours, depending on factors such as the severity of the disaster, transportation challenges, and the condition of the patients. Healthcare staff must be educated and well-trained to follow the following protocol:



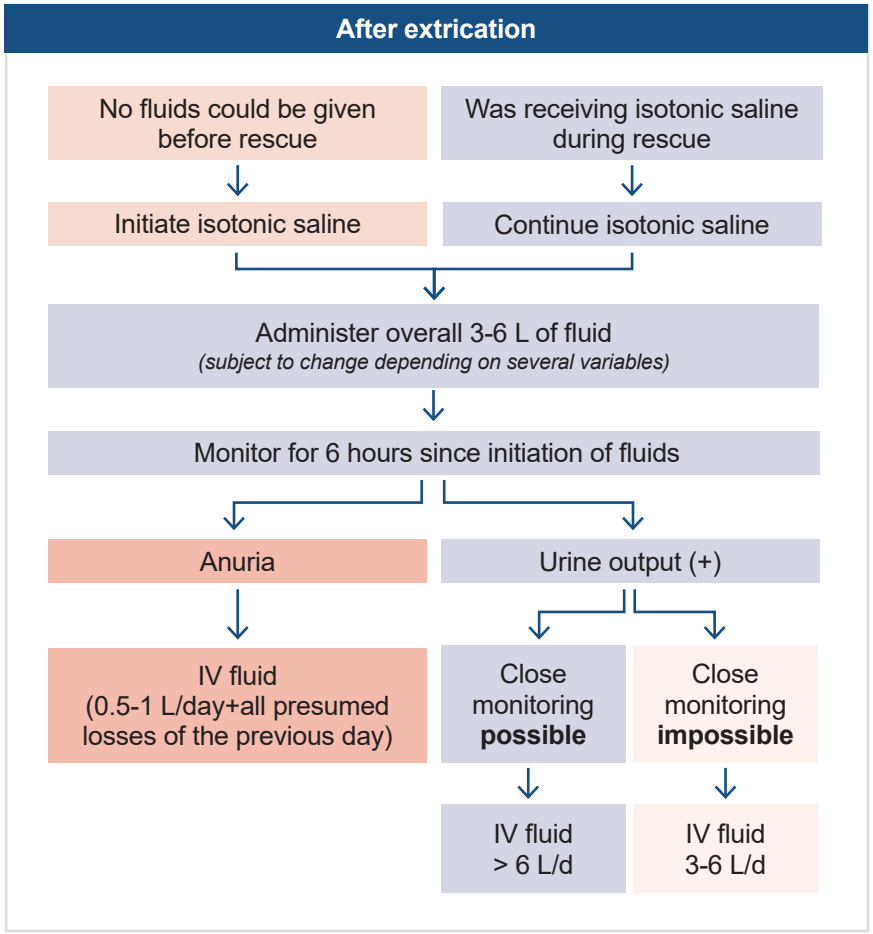


Figure 2: *Fluid administration protocol in adults before, during and after extrication for entrapped victims of mass disasters from "RDRTF of ISN Work Group on Recommendations for the Management of Crush Victims in Mass Disasters" and reproduction of the crush recommendations representing an algorithm for fluid resuscitation to prevent crush-related AKI in entrapped victims of mass disasters early after extrication from Crush Recommendations: a step forward in disaster nephrology.*[4]

Intervention after extrication

Extricated victims should be removed as soon as possible, as the danger of building collapse is high. Healthcare personnel should assess vital signs, determine necessary medical interventions, and conduct triage. Fluid administration and monitoring urine volume are essential in evaluating the health condition of the victims.

Dialysis treatment of crush-related AKI

Renal replacement therapy is necessary for the survival of crush victims with acute kidney injury. Dialysis must be initiated promptly according to absolute indications which include:

- serum potassium ≥ 6.5 mmol/L or rapidly rising serum potassium not responding to other measures
- BUN level ≥ 100 mg/dL (30 mmol/L) or serum creatinine ≥ 8 mg/dl
- uremic symptoms such as volume overload, pericarditis, bleeding, or an otherwise unexplained altered mental status
- continued oliguria or anuria despite adequate fluid resuscitation.[7]

The best treatment option in AKI due to crush syndrome is HD with adequate dialysate flows. The main reasons for this are:

1. To ensure sufficient removal of solutes, especially potassium
2. To allow for a decreased volume of cargo requiring transport
3. To decrease the risk of bleeding.[10]

Conclusion

The long-term consequences of AKI are not widely understood. Numerous studies have shown that a significant number of patients who experienced AKI went on to develop CKD after the initial injury. It is estimated that approximately one in ten of these patients may require chronic dialysis treatment in the subsequent years, which is associated with higher mortality rates.

References

1. Lempert K D, Kopp JB. Hurricane Sandy as a Kidney Failure Disaster. *Am J Kidney Dis*. 2013;61(6):865-868. doi:10.1053/j.ajkd.2013.03.017.
2. Mavrouli M, Mavroulis S, Lekkas E, Tsakris A. The Impact of Earthquakes on Public Health: A Narrative Review of Infectious Diseases in the Post-Disaster Period Aiming to Disaster Risk Reduction. *Microorganisms.*2023;11(2):419 . doi: 10.3390/microorganisms11020419.
3. Fukagawa M. Special Feature:Nephrology Roles and Responsibilites in Natural Disasters Nephrology in Earthquakes: Sharing Experiences and Information. *Clin J Am Soc Nephrol.* 2007;2:803-808. doi:10.1159/000320200.
4. Vanholder R, Sever MS. Crush Recommendations :a step forward in disaster nephrology. *Nephrol Dial Transplant.* 2012;27:1277-1281. doi:10.1093/ndt/gfr666.
5. Sever MS, Vanholder R. Management of Crush Syndrome Casualties after Disasters. *Rambam Maimonides Med J.* 2011;2(2):e0039. doi:10.5041/RMMJ.10039.
6. Shaw R, Shiwaku K, Kobayashi H, Kobayashi M. Linking experience, education, perception and earthquake preparedness. *Disaster Prev Manag.* 2004;13(1):39-49. doi:10.1108/09653560410521689.
7. Sever MS, Vanholder R. Recommendations for the management of crush victims in mass disaster. Nephrology Dialysis Transplantation. Official Publication of the European Renal Association-European Dialysis and Transplant Association; 2012.
8. Yuan CM, Perkins RM. Renal Replacement Therapy in Austere Environments. *Int J Nephrol.* 2011. doi:10.4061/2011/748053.
9. Vanholder R, Sever MS, Smet M De, Erek E, Lameire N. Intervention of the Renal Disaster Relief Task Force in the 1999 Marmara, Turkey earthquake. *Kidney Int.* 2001;59(2):783-91. doi:10.1046/j.1523-1755.2001.059002783.x.
10. Vanholder R, Borniche D, Claus S, Correa-Rotter R, Crestani R, Ferir MC, et al. When the Earth Trembles in the Americas:The Experience of Haiti and Chile 2010. *Nephron Clin Pract.* 2011;117:c184-c197. doi:10.1159/000320200.
11. Muradyan NA, Khachatryan AA, Madoyan TT, Petrosyan RM, Martirosyan AA. The earthquake and the Long-Term Crush Syndrome as a Problem of Health Care Management and Medical Strategy. *J Emerg Intern Med.* 2018;2(2):24.

Chapter 2

Managing end-stage chronic kidney disease in mass disasters during peace

Learning objectives

- To prepare renal nurses for facing a mass disaster
- To guide renal nurses educating patients on how to be prepared for a mass disaster
- To learn about HD patients' emergency self-disconnection through the "Clamp and Cap" technique

Introduction

Worldwide, mass disasters such as earthquakes, typhoons, and floods occur, each presenting unique characteristics. In these large-scale disasters, critical infrastructures such as transportation, communication networks, electricity and water systems, and medical facilities can be significantly damaged. Consequently, the elderly and people with chronic diseases experience heightened stress and vulnerabilities in such challenging circumstances[1].

Among the various chronic disease therapies, dialysis therapy stands out as the most widely utilized life-saving treatment worldwide.[2] However, dialysis units themselves are particularly vulnerable to disruption during emergency situations. This vulnerability arises due to their reliance on specialized medical equipment and their complete dependence on electricity and water systems. A single standard 4-hour dialysis treatment necessitates a substantial volume of 120 litres of purified water.[2]

In this chapter, we will describe the management of people with CKD by health professionals and government authorities following a mass disaster. The primary objective is to minimize health-related losses, protect critical infrastructures and ensure the well-being of healthcare personnel.

Planning before a disaster

Preparedness before a disaster is crucial. All staff members working in medical facilities should receive comprehensive training in how to effectively respond during emergency situations. They should understand their personal responsibilities, maintain composure, prevent panic, and assume control when faced with an emergency. Familiarity with the facility's layout, including the locations of emergency exits and alternative routes, is essential. Additionally, staff should be knowledgeable about the positions of fire extinguishers and receive training on their proper usage. Understanding patient evacuation priorities and identifying a safe meeting place are also important considerations. Finally, staff members must be aware of utility and water shut-off procedures to mitigate potential risk.[3]

For dialysis units, it is crucial to have an emergency box readily available. This box should contain essential documents such as copies of the Medical Evidence Form, HD prescriptions, lists of patients with their contact numbers, lists of staff members phone numbers and emergency contacts, as well as contact numbers of service providers (e.g., suppliers). Additionally, the emergency box should contain a flashlight with spare batteries and a disposable camera for documentation purposes.[3]

By proactively implementing these measures, healthcare facilities can enhance their preparedness for emergencies and ensure the continuity of care for individuals with CKD. The inclusion of relevant documents and essential supplies in the emergency box will facilitate efficient communication and coordination during critical situations.

If a disaster is predicted and an early warning is issued, it is crucial to take proactive measures in managing dialysis therapies for patients. Ideally, dialysis treatments should be completed at least 60 hours before the predicted arrival of the disaster. This timeline allows patients to follow the general population evacuation plans and ensure their own safety. However, for patients who are unable to evacuate, their dialysis therapy should be completed one day before the predicted disaster.

Once the patients have received their necessary treatments, the dialysis unit staff should proceed with their own evacuation. They should gather the emergency box and secure the dialysis facility according to the established

protocol before the staff leave the premises. On the day of the predicted disaster's arrival, the staff should monitor the dialysis unit from a safe location. Continuous communication with state authorities is essential during this time to stay updated on the situation and receive guidance, and decide when is safe to return.[4]

Planning after disaster

Post-disaster planning involves specific actions to be taken by dialysis units to ensure the safety and well-being of staff, patients, and visitors. In the event of an evacuation, everyone should be guided to a safe meeting point, where a head count must be conducted. If any individuals are found to be missing, a thorough search of the building should be carried out if it is deemed safe to do so. In cases where individuals cannot be located, the first responders should be promptly informed about the missing persons. Additionally, a command center should be established to coordinate the response efforts, and patients should be informed about potential interruptions to their treatment and the expected duration. Emergency plans should be activated to address any critical situations that may arise.[3]

Water supply is vital for dialysis units to provide renal replacement therapy. After a disaster, the local municipal distribution system may be disrupted. If the delivered water is safe for consumption, it can also be used for the water treatment system in the dialysis unit. It is important to determine whether fire hydrants, which often have a separate water line, provide potable water.[3]

If the dialysis unit building remains unaffected by flooding and safe water is available, the dialysis machines must undergo chemical disinfection and rinsing before reuse. The disinfectant levels must be carefully tested to ensure proper rinsing. Subsequently, the conductivity of the machines should be adjusted, and a self-test performed to verify their proper functioning. If any machine fails the self-test, it should be repaired before being put back into use.[5]

By following these post-disaster protocols, dialysis units can effectively manage the aftermath of a disaster, ensure the availability of safe water, and maintain the functionality of dialysis machines for the continued provision of crucial renal replacement therapy.

Patient evaluation in disaster settings

In disaster settings, the evaluation of renal patients becomes crucial for providing appropriate medical care. In the context of disaster response, the equipped medical facilities are of paramount importance as they will act as a base for medical personnel or first responders to assess the health condition of these patients. The evaluation process is based on various factors, including the patient's medical history, physical examination, and diagnostic testing.[6] Studies have shown that the severity of crush syndrome in patients is often underestimated, particularly when the patient is conscious. To overcome this challenge, the use of mobile instruments that measure key parameters such as haematocrit, base deficits and potassium concentrations can significantly aid in assessing the severity of the condition.[7]

To streamline the assessment and prioritization of renal patients in disaster settings, a dialysis triage system can be implemented in disaster medical facilities. This triage system is based on a numbering system in order to avoid confusion with color-based triage systems typically used in emergency departments.

The dialysis triage levels are as follows:
Triage 1: Patients requiring immediate dialysis with hospital admission
Triage 2: Patients requiring immediate dialysis without hospital admission
Triage 3: Patients requiring dialysis within 12-24 hours
Triage 4: Patients requiring dialysis within 24-48 hours
Triage 5: Patients who are not likely to require dialysis[6]

Education of patients prior to a disaster

Prior to a disaster, it is essential to educate chronic dialysis patients on how to effectively respond during such situations. Patients undergoing haemodialysis (HD) should receive comprehensive training that covers various aspects. The educational program should include:

1. Nutritional plan: Patients should be educated about their specific nutritional needs and how to manage their diet during a disaster. This includes understanding dietary restrictions, portion control, and ensuring adequate nutrition intake.
2. Fluid control: Proper fluid management is crucial for dialysis patients. They should be taught how to monitor and regulate their fluid intake, especially in emergency situations where access to clean water may be limited.
3. Emergency disconnection: Patients should be familiarized with the process of disconnecting from the dialysis machine during an emergency. They should understand the steps involved in safely detaching themselves from the equipment.
4. Personal evacuation plan: Each patient should have a personalized evacuation plan that outlines the necessary steps to take in case of a disaster. This includes identifying safe evacuation routes, knowing the location of emergency exits, and understanding how to reach the designated safe meeting place.

Clamp and Cap / Clamp and Cut procedure: In the event of an immediate evacuation of the dialysis unit, patients need to be aware of the Clamp and Cap procedure. This procedure involves:

- locating the emergency pack containing necessary supplies
- clamping both lines which are directly connected to the needles or catheter
- clamping both thicker bloodlines
- if the lines have pinch clamps, fully closing all four pinch clamps
- unscrewing the lines between the closed clamps and capping the ports of the lines still connected to the catheter or needles

NEVER cut the access needle lines or between the clamp and the access.
Catheters lines should NEVER be cut under any circumstances.[3]

Clamp and Cut procedure

According to protocols, only patients with arteriovenous fistula (AVF) or arteriovenous graft (AVG) can be trained in emergency patient "self-disconnection" procedure. According to "Clamp and Cut" technique, patients should be able to face and reach a rotating screen of the HD machine and have access to the emergency kit which contains a cutting tool. Patients should always be able to reach this kit during the dialysis procedure.

Self-disconnection training follows 3 steps:

Step 1	**Stop the HD machine blood pump.** The patients get trained to use their free hand to press the Stop button to terminate the HD session on the screen of the HD machine.
Step 2	Clamp the clips on all 4 lines: 2 vascular access lines and 2 bloodlines
Step 3	Cut between the closed clips. Patients should be very careful **never to cut the access needle lines between the clamps and the access**.[8]

Chronic patients on PD: The education plan for patients on PD should include specific training covering the following aspects:

1. Functioning under nonhygienic conditions: Patients should be educated on how to perform dialysis in nonhygienic conditions, as access to clean water and a sterile environment may be compromised during a disaster. They need to understand the necessary precautions and adaptations to maintain the best possible hygiene and safety standards.
2. Emergency disconnection from automated PD machine: Patients must be trained on how to disconnect from the automated PD machine in case of an emergency. They should be familiar with the steps involved in safely detaching themselves from the equipment and ensuring proper storage of the necessary medical materials.[9]

Conclusion

All dialysis facilities should develop comprehensive emergency plans to ensure preparedness for potential disasters. This includes providing training to both facility personnel and patients on how to effectively respond during emergency situations through regular emergency drills. Patients should be well informed and prepared regarding the facility's plan for accessing dialysis treatments in the event of a disaster. Finally, it is crucial for every dialysis unit to prioritize adequate disaster planning, effective communication, and periodic re-assessment of these plans to maintain their effectiveness.[5]

References

1. Lempert K, Kopp JB. Renal Failure Patients in Disasters. *Disaster Med Public Health Prep*. 2019;13(4):782-790. doi:10.1017/dmp.2018.142.
2. Piccoli G, Pacitti A, Mangiarotti G, Jeantet A, Mezza E, Segoloni GP, et al. Blade Runner, blackout and haemofiltration: dialysis in times of catastrophe. *Nephrol Dial Transplant.* 2005;20(3):663-4. doi:10.1093/ndt/gfh623.
3. Disaster Preparedness-A Guide for Chronic Dialysis Facilities Second Edition. CMS (Centers for Medicare&Medicad Services).
4. Kopp JB, Ball LK, Cohen A, Kenney RJ, Lempert KD, Miller PE, et al. Kidney Patient Care in Disasters: Emergency Planning for Patients and Dialysis Facilities. *Clin J Am Soc Nephrol.* 2007;2:825-838. doi: 10.2215/CJN.01220307.
5. What if Disasters Happens here? Questions and Answers Based on lessons learned from past disasters For the Renal Community Prepared by Northwest Renal Network Developed by the Heartland Kidney Network (ESRD Network). 2007.
6. Lempert KD, Kopp JB. Renal Failure Patients in Disasters. *Disaster Med Public Health Prep.* 2019;(4):782-790.doi:10.1017/dmp.2018.142.
7. Kubota M, Ishida H, Kojima Y, Fukuda A, Mizushima Y,Mizobata Y, et al. Impact of Mobile Clinical Analyzers on Disaster Medicine: A Lesson From Crush Syndrome in the 1995 Hanshin-Awaji Earthquake. *Biomed Instrum Technol.* 2003;37:259-262.
8. Liossatou A, Golland E. Disaster preparedness and evacuation plan (DPEP) in haemodialysis units: patients' emergency self-disconnection through "Clamp and Cut" procedure. E-Library article, EDTNA/ERCA, 2021.
9. Sever MS, Vanholder R. Recommendations for the management of crush victims in mass disaster Nephrology Dialysis Transplantation. Official Publication of the European Renal Association-European Dialysis and Transplant Association;2012.

Chapter 3

Managing Acute Kidney Injury (AKI) and Chronic Kidney Disease (CKD) in wartime

Learning objectives

- To raise awareness of the importance of establishing appropriate protocols in renal units during wartime
- To prepare healthcare personnel managing renal patients during wartime

Introduction

Combat-related renal failure is unusual; however, this poses a greater threat to individuals due to limited treatment options compared to routine conditions. Despite the fact that crush-related renal failure has been studied dating back to World War II and the Korean War, there is a scarcity of research regarding the impact of war and conflict on dialysis and transplant patients. This chapter aims to provide a reference for renal support options during times of conflict and wartime.

Managing Chronic Kidney Disease during wartime

Conflicts are responsible for disrupted renal facilities, which impacts the medical care of patients requiring renal replacement therapy. The absence of dialysis therapy for these patients can rapidly lead to fatal outcomes within a few days. Additionally, transplant patients face the risk of acute rejection if they are unable to receive their anti-rejection medication. Reports consistently highlight higher mortality rates among people with CKD during wartime due to the shortened duration of dialysis therapy and limited triage of care.[1]

War operations have extensive and profound consequences, including creating a significant number of refugees, among whom there may be individuals with CKD or who have undergone transplantation. War can also lead to a scarcity of medical staff, non-functioning medical facilities, shortages of medications and medical supplies, and a lack of access to

electricity and clean water.[1] It has been estimated that refugees in Europe and the Middle East make up approximately 1.5% of dialysis patients in renal facilities.[2] In situations such as the war in Syria, the medical response involved the contribution of volunteer nurses and nephrologists from other countries, as well as the use of telemedicine as it is a low-cost way of providing medical care in a country under war, keeping healthcare personnel safe.[1,3]

Managing Acute Kidney Disease in wartime

Cases of AKI following combat trauma were rarely recorded before World War II likely because patients died from hypovolemic shock before developing AKI. However, during World War II, there was an increasing number of reports of civilians developing crush syndrome after the bombing in cities, as well as military personnel developing AKI after someone has resuscitated them.[4] The incidence of AKI in combat injuries varied across different war operations, with rates of nearly 20% in previous conflicts, 0.5% in Korea, 0.17% in Vietnam and 13-34% in Iraq. These variations were attributed to differences in war tactics, medical care capabilities, and the duration of transit from the field to advanced medical facilities.[5]

During World War II, extended trauma to soldiers was leading to AKI attributing to a mortality rate of 90%.[3] However, with the initiation of HD therapy in Korea, this percentage was decreased to 68%.[3] Various factors contributed to this gradual decrease in mortality. These factors included the use of reinforced body arm or, soldiers trained in first-aid techniques, the application of tourniquets, the utilization of intraosseous needles, and the efficient evacuation of patients through helicopter transport.[3]

HD therapy requires significant amounts of water, skilled healthcare professionals, and appropriate equipment. Fortunately, advancements in technology have led to the development of home dialysis equipment that addresses these requirements. The machines used for home dialysis are portable, lightweight, and most importantly, can be easily transported by helicopter or plane. However, it is important to note that this new equipment has not yet been included in standard military stock.[3]

Conclusion

While there are often healthcare professionals, such as the Renal Disaster Relief Task Force (RDRTF), volunteering their services after natural disasters like earthquakes, the situation is quite different in conflict areas due to the severe security risks involved. War operations can last for an unknown period of time, resulting in an unpredictable number of refugees, a shortage of medical staff and financial challenges. Therefore, addressing the needs of the affected population requires collaboration among international and regional organisations, governments, non-governmental charities, the United Nations, the renal industry, and other relevant stakeholders.[1,6]

Regarding the capability of providing renal replacement therapy in military field settings, it is important to note that the necessary equipment is not included in the deployed hospital packages of all countries. The nature of the next war theater remains unknown, but it may resemble the conditions experienced during World War II, characterized by delayed evacuation, prolonged hypotension, and inadequate resuscitation, all of which are risk factors for AKI. Therefore, research and development efforts should focus on creating systems that can generate fluids in the field and new renal replacement therapy (RRT) systems that require minimal fluids, such as home modalities.[4]

References

1. Isreb MA, Rifai AO, Murad LB, Al-Makki A, Al-Saghir FA, Sekkarie MA. Care and outcomes of end-stage kidney disease patients in times of armed conflict: recommendations for action. *Clin Nephrol.* 2016;85(5):281-8.doi:10.5414/CN108795.
2. Isreb MA, Kaysi S, Riffai AO, Kukhun HA, Al-Adwan SAS, Kass-Hout TA, et al. The effect of War on Syrian Refugees With End-Stage Renal Disease. *Kidney Int Rep*. 2017;2(5):960-963. doi:10.1016/j.ekir.2017.05.009.
3. Vanholder R, Gallego D, Sever M S. Wars and kidney patients: a statement by the European Kidney Health Alliance related to the Russian-Ukrainian conflict. *J Nephrol.* 2022;35(2):377-380.
4. Nesbitt I, Almond MK. Renal Support in Military Operations. Combat Anesthesia The First 24 Hours. (pp321). Office Of the Surgeon General, Borden Institute.2015.
5. Hoareau GL, Beyer CA, Walker LE, Chung KK, Stewart IJ. Renal Replacement Therapy Capability for the Treatment of Combat-Associated Acute Kidney Injury: A Historical Perspective to Plan for Future Conflicts. *Military Medicine.* 2019;184,3/4:81.
6. Tuğlular, S., Luyckx, V., Vanholder, R., Skoberne, A., Wiecek, A., Nistor, İ., & Renal Disaster Relief Task Force of the ERA. (2023). Lessons learnt during the war in Ukraine: a report from The Renal Disaster Relief Task force of ERA. *Nephrology Dialysis Transplantation*, gfad053.

Chapter 4

Acute Kidney Injury in chemical warfare

Learning objectives:

- To clarify the toxicity and hazards emerging today from a massive chemical warfare exposure, whether to military or civilian targets
- To define the measures necessary in a Renal Unit during a massive chemical warfare exposure

Introduction – Chemical warfare agents

Chemical warfare agents include several compounds that are capable of causing mass poisoning casualties. International law and United Nations (UN) treaties forbid the development, production, stockpiling, and use of chemical warfare.[1] According to the Chemical Weapons Convention (CWC), held by the Organisation for the Prohibition of Chemical Weapons (OPCW, The Hague, Netherlands), the majority of the declared chemical weapons stock were destroyed by the end of 2020.

Nevertheless, large amounts of various agents remain available, about 1200 tones worldwide, according to the CWC report.[1,2] In addition, many chemicals not prohibited by the CWC either have the potential to cause mass casualties or are precursors for the easy production of chemical weapons. In this context, the use of chemical weapons against military or civilian targets has been reported several times in the last few decades. A special concern exists for their use in civilian terrorism.[3]

Each compound that has been identified for use in chemical warfare has a certain 1-3-character code assigned by the North Atlantic Treaty Organisation (NATO) (also called the NATO codes). Some are known mainly by this code rather than by the chemical name, e.g., VX for O-ethyl S-[2-(diisopropylamino) ethyl] methylphosphonothioate or BZ (or QNB) for 3-quinuclidinyl benzilate.

Chemical weapons are classified in the following categories based on their mode of action.[2-4] Each of the chemical weapons in these categories acts by certain mechanisms and induces specific set of symptoms that we

refer to as a syndrome (e.g., toxic syndrome). Familiarisation with these syndromes can help with the identification of the chemical compound.[4]

Nerve agents: Tabun (GA), Sarin (GB), Soman (GD), Cyclosarin (GF), VX (O-ethyl S-[2-(diisopropylamino)ethyl] methylphosphonothioate), and Novichok. All of these belong to a group of compounds known as anticholinesterases and they have additional effects at muscarinic and nictonic receptors, resulting in central nervous system (CNS) symptoms. This can induce an acute cholinergic crisis with coma, seizures, paralysis, and lung distress or apnea. Cholinergic symptoms are typical but differ depending on the root of exposure. Vapour inhalation induces mainly miosis, rhinorrhea, salivation, and dyspnoea, while liquid skin contact induces localised sweating, twitching, and fasciculations.[4]

Cyanide compounds (formerly "blood" agents) Cyanide (AC) induces cytochrome oxidase inhibition, cellular anoxia, and lactic acidosis. Symptoms include progressive tachypnoea, coma, seizures, and apnea.[4]

Vesicant agents Mustard compounds, i.e., sulphur mustard [H] (alkylating agents that additionally induce bone marrow toxicity) and Lewisite (L) (which additionally induces systemic multiorgan toxicity), induce skin erythema, vesicles, eye inflammation, and respiratory tract inflammation.[4]

Incapacitating agents: BZ (3-quinuclidinyl benzilate), is a competitive acetylcholine antagonist that acts at the muscarinic receptors. These induce typical anticholinergic symptoms such as mydriasis, xerostomia, flushed skin, hypertension, absent bowel sounds, retention of urine, delirium and seizures.[4]

Pulmonary agents. Type I agents (hydrogen chloride or hydrogen fluoride) cause central respiratory irritation with laryngospasm and airway obstruction; type II agents, such as phosgene [GG] cause pulmonary oedema. Combination agents, e.g., chlorine, cause both type I and II reactions.

It is obvious that exposure to any of the above compounds can lead to life-threatening systemic toxicity, and can induct septic shock, hypoxia, and multi-organ failure. Multiorgan failure is frequently accompanied by severe AKI requiring renal replacement therapy.[5] In this context, nephrology services and renal replacement units may be involved in the treatment of people who have been exposed to chemical weapons.

This chapter will cover the rules and action plans for renal units and healthcare professionals in the event of treating a person who has been exposed to a chemical weapon.

General measures for chemical disasters

The main principles of management in chemical disasters aim to avoid spreading the hazard and contamination, especially to hospitals, as well as reduce overall morbidity and mortality. All health care providers should be familiar with the general principles of management in chemical disasters (Table 1).

***Table 1**. The general principles of management in chemical warfare exposure and other chemical disasters[4,12]*

Immediate actions in massive chemical exposure incidents
Readily recognise the existence of a chemical exposure.
Notify the authorities and establish a local and on-site incident command.
Define the affected area and control entry to and exit from it.
Determine the toxic compound involved.
Apply rigorous self-protection and decontamination.
Decontaminate casualties to reduce their exposure and avoid the spread of hazards.
Stabilise and triage casualties.
Apply as soon as possible an antidote treatment if one is available.
Ensure decontamination of victims leaving the area (by detectors if available).
Ensure ongoing monitoring for victims released or transported for further treatment.

The first step is to readily recognise the existence of a chemical exposure and notify the authorities. There are certain characteristics that enable a clinician to recognise chemical mass incidents and exposure to chemical weapons (Table 2). A local and on-site incident command should be established, and the movement into and out of the affected area should be rigorously controlled.

Table 2. *Characteristics that should lead clinicians and, generally, health care professionals to suspect mass exposure to a chemical or biological warfare agent*[4,13]

	Chemical agent	Toxins	Biological agents
Unexplained deaths*	Yes	Yes	Yes
Timing and location of symptomatic victims	Simultaneous, same location	Simultaneous, same location	Dispersed in time and location
Onset of symptoms	Mostly rapid (min)	Delayed (hours)	Delayed (days)
Smoke or fog	Often	No (except mycotoxins)	No
Blisters	Mustard compounds, Lewisite	Mycotoxins	Some agents
Dyspnoea	Often	Often	Often
Neuromuscular effects (e.g., seizures)	Nerve agents and cyanide compounds	Botulinum toxin	No
Fever	No	No	Yes
Rash	No	Rare	Often
Bleeding	Uncommon	Some cases	Common

*Unexplained deaths of humans, animals, fish, or plants

Chemical vapours may be invisible. Moreover, liquid chemical weapons may take hours to be absorbed and cause symptoms.

As soon as possible, the toxic compound involved should be identified using available information, typical symptoms, or laboratory findings. Rigorous self-protection and casualty decontamination are most important to reduce exposure and avoid the spread of hazards. In parallel, stabilisation and triage of casualties should follow according to previously defined specific principles for mass casualty triage.[6,7] Before release or transport to medical treatment facilities, decontamination of victims should be ensured (if available by specialised detectors). An antidote treatment should be administered as soon as possible, if available.

Patients who develop AKI may need to be treated in hospital with dialysis or other renal replacement therapies. Severe AKI is mostly a late complication of chemical exposure, and casualties treated in renal units are those who have survived at least the first few hours of chemical exposure, have been adequately decontaminated, and have had received an antidote treatment.

Nevertheless, the management of chemical agent poisoning is an ongoing process, and nephrology care providers have to be aware of the hazards, typical symptoms, and potential complications of chemical compound poisoning. Administration of an antidote and supportive treatment should be continued during renal replacement therapy if required (Table 3).

Table 3. *Initial management of casualties exposed to chemical weapons, describing roughly the decontamination measures and administration of antidotes*

Chemical weapon category	Decontamination	Therapy, Antidote
Nerve agents	Vapour agents: Move to fresh air, remove clothes, wash hair. Liquid agents: Remove clothes, irrigate skin with water or soapy water, and clean eyes and wounds with sterile saline or water. Reactive skin decontamination with liquid for spot decontamination	Administer by suspicion: Atropine (2 mg), pralidoxime (600 mg) for rising severity, and benzodiazepines (Diazepam 10 mg) for seizures.
Cyanide compounds (formerly "blood" agents)	Fresh air and soapy water for the skin.	By suspicion, administer hydroxocobalamin or amyl nitrite (inhalation) and sodium nitrite and sodium thiosulfate (iv) if hydroxocobalamin is unavailable.

Chemical weapon category	Decontamination	Therapy, Antidote
Mustard compounds	Soapy water for the skin; water for the eyes (effective only within minutes of exposure).	Symptomatic care as it is practised in burns, corneal toxicity, and bone marrow suppression
Lewisite (L)	Skin: Soap and water Eyes: Water (effective only within minutes of exposure)	Symptomatic care as for burns. In severe cases, the antidote is dimercaprol (British anti-Lewisite; BAL), 3–4 mg/kg/4-6 h i.m.
BZ (3-quinuclidinyl benzilate)	Irrigate the skin with water or soapy water	Benzodiazepines for agitation. Physostigmine is for patients with moderate to severe anticholinergic effects (e.g., delirium or seizures).
Pulmonary agents, type I agents	Move into fresh air and irrigate the skin with water.	Humidified oxygen. Inhaled epinephrine for upper airway obstruction. Pulmonary toilet and bronchoscopy for severe upper airway obstruction
Pulmonary agents, type II, or combination agents	Move into fresh air and irrigate the skin with water.	High-flow nasal cannula, nasal CPAP, or positive pressure ventilation. Pulmonary ICU. For combination agents, treatment is the same as for type I and type II pulmonary compounds.

Specific measures and management in Renal Units

Renal units in hospitals that are receiving victims of a chemical attack are principally integrated into the disaster management plan of the facility. However, renal units should have their own emergency plan (Table 4).

Table 4. *Specific measures and management of chemical weapons mass exposure in renal units*

Management of chemical weapons mass exposure in Renal Units
Elaborate Renal Unit emergency plan for chemical mass exposure.
Define a separate room for the treatment of casualties.
Consider the transfer of dialysis patients for chronic treatment.
Appoint a disaster-specific liaison and a safety.
Remain fully informed about all management (e.g., antidote treatment) procedures.
Apply rigorous self-protection to staff and decontamination measures.
Consider continuous treatment* in the ICU for AKI with multiorgan failure.
A relevant elimination of chemical warfare agents by haemoperfusion cannot be supported; nevertheless, in cases exposed to anticholinesterases, the application of haemoperfusion methods is the rule.

*Continuous Veno-Venous Haemofiltration (CVVH), Haemodialysis (CVVHD), or Haemodialfitration (CVVHDF)

The first step of such a management plan is to consider transferring patients receiving maintenance dialysis and answer the critical question of whether these patients in the hospital renal unit should be sent for treatment to other facilities. This decision is based first on the proximity of the hospital to the affected area and the atmospheric contamination, and second on the capability of the renal unit to treat casualties. A separate area in the renal unit is needed to adequately treat victims without putting patients on chronic HD at risk of contamination or a treatment of reduced quality. The unit's capability should be continually assessed in order to maintain staff safety and adequate treatment for both victims and patients on chronic HD. Patients on PD should be advised to avoid routine unit visits until casualties and spot decontamination are considered complete.

It is recommended that, among the group of highly experienced personnel, an individual be promptly designated as the individual responsible for ensuring safety during disaster scenarios. This appointment would aid the management in effectively minimising the contamination hazard. It is advised that an additional individual be designated as a liaison to effectively facilitate communication with the authorities responsible for disaster management. Effective communication is crucial in facilitating the timely dissemination of information and generally will ensure an integrated response to the chemical exposure. For example, the identity and detection method of the poisonous chemical compound are valuable pieces of information. In this way, adequate medical treatment, including antidote therapy, can be provided.

Self-protection measures are essential in cases of chemical contamination, and health care providers should have previously received adequate education and practise on these measures. Unit staff in contact with contaminated patients should use personal protective equipment (PPE). Level C protection, with a full-body chemical-resistant suit, double gloves, shoe covers, and an air-purifying respirator (APR), is sufficient in this situation.

Care of victims in the renal unit

Patients who develop AKI are frequently in a serious condition with multiorgan failure, which is generally induced by serious hypoxia and shock. This condition is frequently associated with low blood pressure and continuous methods of renal replacement therapy. Continuous Veno-Venous Haemofiltration (CVVH), Haemodialysis (CVVHD), or Haemodialfitration (CVVHDF) are preferred to intermittent HD or other intermittent treatment methods. AKI is a relatively frequent complication; however, it typically appears later in people who have survived an acute exposure. The application of continuous treatment methods should take place in the ICU, and staff on the renal unit may not be involved or may be only partially involved in treatment. The need for self-protection in the ICU should be adapted accordingly.

Treatment with antidotes and removal methods

Antidotes are available for certain chemical weapons, nerve agents, cyanide compounds, and BZ (Table 3). Antidotes should be administered within minutes or hours after exposure. The staff of the renal unit should be informed about any antidote administration and about potential contraindications with kidney impairment or interactions with renal replacement therapies.

Haemofiltration, continuous haemofiltration, and high-flux HD are not effective methods for the removal of any chemical warfare agent.[8,9] They may all be used only as renal replacement therapy (RRT) in cases of AKI. The immediate binding of these agents to albumin and other high-molecular-weight proteins in plasma, together with their extended tissue distribution, explain the ineffectiveness of both HD and haemofiltration in their removal. Even in the case of continuous application of haemofiltration, which takes advantage of a long-lasting and thus more extended tissue plasma redistribution, effectiveness has been very limited.[8,9]

There are reports about the use of charcoal and resin haemoperfusion for various anticholinesterase agents with limited clinical impact. In an animal study with experimental VX and sarin intoxication haemoperfusion was shown to be only partially effective. Passing the patients' blood (haemo-) through a resin or charcoal filter (-perfusion) leads to the adsorption of chemical substances (ionic or not) upon the filter, resulting in their removal from the blood. The substances we discuss here (chemical warfare) are adsorbed and thus removed from blood. However, the effectiveness of the removal by haemoperfusion is also limited because the chemicals are immediately widely distributed in the tissues (they do not remain in the blood).[10,11]

Conclusion

The Renal Unit staff, like every other health care professional, should be aware of a chemical mass exposure and be familiar with the management of chemical exposure (Table 1).

Hospital renal units should have their own emergency plan for chemical mass exposure. The room for treatment of casualties should be separate from that of non-contaminated patients. In order to avoid any unintentional contamination, the transfer of chronic dialysis patients might be needed. The self-protection of staff and decontamination measures should be rigorous. AKI as a complication of chemical exposure appears in casualties with multiorgan failure who survived acute exposure and who frequently need treatment in the ICU.

Useful links about Chemical Hazards

- European Medicines Agency (EMA), Committee on Proprietary Medicinal Products (CPMP). Guidance document on the use of medicinal products for the treatment of patients exposed to terrorist attacks with chemical agents. https://www.ema.europa.eu/documents/other/european-medicines-agency/committee-proprietary-medicinal-products-guidance-document-use-medicinal-products-treatment-patients_en.pdf
- Chemical Hazards Emergency Medical Management (CHEMM) https://chemm.hhs.gov/
- Personal Protection Equipment [PPE] defined by the Occupational Safety and Health Administration (OSHA) https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.120AppB.
- Agency for Toxic Substances and Disease Registry (ATSDR). Managing Hazardous Materials Incidents (MHMIs). https://www.atsdr.cdc.gov/mhmi/
- Warfare and Terrorism Agents (used in acts of war or terror). https://wwwn.cdc.gov/TSP/substances/ToxChemicalListing.aspx?toxid=34

References

1. Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Warfare Weapons and on their Destruction in 2020 (Chemical Weapons Convention): https://www.opcw.org/chemical-weapons-convention (accessed 31st January 2023)
2. Pitschmann V, Hon Z. Drugs as Chemical Weapons: Past and Perspectives. *Toxics*. 2023;11:52. doi: 10.3390/toxics11010052
3. Okumura T, Suzuki K, Fukuda A, Kohama A, Takasu N, Ishimatsu S, Hinohara S. The Tokyo subway sarin attack: disaster management, Part 2: Hospital response. *Acad Emerg Med*. 1998;5:618-24. doi: 10.1111/j.1553-2712.1998.tb02471.x.
4. Prockop LD. Weapons of mass destruction: Overview of the CBRNEs (Chemical, Biological, Radiological, Nuclear, and Explosives). *J Neurol Sci*. 2006;249(1):50-4. doi: 10.1016/j.jns.2006.06.017.

5. Srivastava RK, Traylor AM, Li C, Feng W, Guo L, Antony VB, Schoeb TR, Agarwal A, Athar M. Cutaneous exposure to lewisite causes acute kidney injury by invoking DNA damage and autophagic response. *Am J Physiol Renal Physiol.* 2018;314(6):F1166-F1176. doi: 10.1152/ajprenal.00277.2017.
6. Benson M, Koenig KL, Schultz CH. Disaster triage: START, then SAVE--a new method of dynamic triage for victims of a catastrophic earthquake. *Prehosp Disaster Med.* 1996;11(2):117-24. doi: 10.1017/s1049023x0004276x.
7. SALT mass casualty triage: concept endorsed by the American College of Emergency Physicians, American College of Surgeons Committee on Trauma, American Trauma Society, National Association of EMS Physicians, National Disaster Life Support Education Consortium, and State and Territorial Injury Prevention Directors Association. *Disaster Med Public Health Prep*. 2008;2(4):245-6. doi: 10.1097/DMP.0b013e31818d191e.
8. Moshiri M, Darchini-Maragheh E, Balali-Mood M. Advances in toxicology and medical treatment of chemical warfare nerve agents. *Daru.* 2012;20(1):81. doi: 10.1186/2008-2231-20-81.
9. Roberts DM, Aaron CK. Management of Acute Organophosphorus Pesticide Poisoning. *BMJ*. 2007;334(7594):629-34.
10. Yokoyama K, Ogura Y, Kishimoto M, Hinoshita F, Hara S, Yamada A, Mimura N, Seki A, Sakai O. Blood purification for severe sarin poisoning after the Tokyo subway attack. *JAMA*. 1995;274(5):379.
11. Monhart V, Fusek J, Brndiar M, Tlustakova M. Use of hemoperfusion in experimental intoxication with nerve agents. *Artif Organs*. 1994;18(10):770-2. doi: 10.1111/j.1525-1594.1994.tb03317.x.
12. Chemical Hazards Emergency Medical Management (CHEMM). https://chemm.hhs.gov/ (accessed 31st January 2023)
13. Madsen JM. Toxins as weapons of mass destruction. A comparison and contrast with biological-warfare and chemical-warfare agents. *Clin Lab Med.* 2001;21:593-605

Chapter 5

Acute Kidney Disease in biological war

Learning objectives:

- To define known biological agents and recognise emerging hazards in the case of biological warfare agent exposure to military or civilian targets
- To define the measures necessary in a renal unit during a biological warfare

Introduction – Biological warfare agents

Biological weapons mainly include disease-causing microorganisms (bacteria, viruses, and fungi) and biotoxins. The microorganisms can be either in their natural form or genetically modified. They harm humans, animals, or plants and can be deadly and highly contagious. The intentional release and dissemination of these agents in order to harm the enemy is the biological warfare.[1,2]

Diseases caused by biological weapons can spread rapidly, independent of any national borders, and the consequences might be disastrous. Biological warfare agents are also suitable for terrorist use because they are relatively easy to manufacture, conceal, transport, and release. Small amounts can cause great harm and high mortality.[1,2]

United Nations (UN) treaties effectively forbid the development, production, acquisition, transfer, stockpiling, and use of biological weapons. The Biological Weapons Convention (BWC) has established a strong norm against biological weapons. This UN multilateral treaty was developed in 1972 and has reached almost universal acceptance today, with 185 state parties in total.[1]

The US Centres for Disease Control (CDC) have identified a number of biological weapons that could also be used in terrorism and have ranked them into categories (A, B, and C) based on their public health priority, i.e., their overall potential to cause harm.[2,3]

Category A includes high-priority agents that can be easily disseminated (airborne dissemination), can be grown in large quantities, are resistant to treatment, result in high mortality rates, and have an overall major public health impact. Characteristic examples are anthrax and viral haemorrhagic fever (Table 1).

Table 1. *Potential agents of biological war separated under the categories defined by the US Center of Disease Control,[2,3] according to their public health priority, i.e. their overall potential to cause harm.*

Category A	Category B	Category C
Anthrax *(Bacillus anthracis)*	Brucellosis (*Brucella* species)	Hantavirus
Plague *(Yersinia pestis)*	Glanders *(Burkholderia mallei)*	Nipah virus
Smallpox *(Variola major)*	Melioidosis *(Burkholderia pseudomallei)*	Yellow fever
Tularaemia *(Francisella tularensis)*	Q fever *(Coxiella burnetii)*	Multidrug-resistant tuberculosis
Botulism (*Clostridium botulinum* toxin)	Psittacosis *(Chlamydia psittaci)*	Tickborne encephalitis virus
Viral hemorrhagic fevers	Typhus fever *(Rickettsia prowazekii)*	Tickborne haemorrhagic fever virus
Filoviruses (Ebola, Marburg)	Alphaviruses (eastern, Venezuelan, and western equine encephalitis)	
Arenaviruses (Lassa, Machupo)	Water safety threats *(Vibrio cholerae, Cryptosporidium parvum)*	
	Food safety threats *(Salmonella* species, *Escherichia coli* O157:H7, *Shigella*)	
	Epsilon toxin of *Clostridium perfringens*	
	Ricin toxin (from castor beans)	
	Staphylococcal enterotoxin B	

Category B, the second highest priority agent, is less easy to disseminate than the previous category, results in moderate-grade morbidity and mortality, and may require enhanced diagnostic capacity or surveillance techniques. Brucellosis and *Escherichia coli* O157:H7 are some examples (Table 1).

Category C includes the third-highest priority agents, which are emerging pathogens that could easily be made to be released on purpose and spread to a large number of people in the future. This is because they are available, easy to make, and could cause a lot of death and illness. Examples are Hantavirus and multi-drug-resistant *Mycobacterium tuberculosis* (Table 1).

Severe infections lead to life-threatening systemic disease, generally in the form of septicaemia and multiorgan failure. Septic shock and multiorgan failure are conditions frequently accompanied by severe AKI requiring renal replacement therapy. In addition, there are certain infectious agents, such as Hantavirus infection, that can cause interstitial nephritis, expressed as AKI. In this context, it is easy to see that nephrological clinics and renal replacement units would very often be involved in the treatment of such victims.

The content of this chapter deals exactly with this issue, namely, the rules and the action plan suitable for renal units and nephrology health care professionals in case of biological warfare agent exposure.

General measures for the management of biological disasters

The main target of management in biological warfare events is to control the spread of contamination and reduce overall morbidity and mortality. The first step is to recognise the mass exposure to a biological warfare agent in time in order to avoid the disaster.[4] In contrast to chemical warfare agents, which are visible and lead to rapid local spread, biological weapons are frequently invisible and lead to a slow accumulation of casualties (Table 2).[4]

***Table 2**. Characteristics that should lead clinicians and, generally, health care professionals to suspect mass exposure to a chemical or biological warfare agent[4,13]*

	Chemical agent	Toxins	Biological agents
Unexplained deaths*	Yes	Yes	Yes

	Chemical agent	Toxins	Biological agents
Timing and location of symptomatic victims	Simultaneous, same location	Simultaneous, same location	Dispersed in time and location
Onset of symptoms	Mostly rapid (min)#	Delayed (hours)	Delayed (days)
Smoke or fog	Often#	No (except mycotoxins)	No
Blisters	Mustard compounds, Lewisite	Mycotoxins	Some agents
Dyspnoe	Often	Often	Often
Neuromuscular effects (e.g. seizures)	Nerve agents, cyanide compounds	Botulinum toxin	No
Fever	No	No	Yes
Rash	No	Rare	Often
Bleeding	Uncommon	Some cases	Common

** Unexplained deaths of humans, animals, fish, or plants*
 # Chemical vapors may be invisible. Moreover, liquid chemical weapons may take hours to be absorbed and cause symptoms.

Timely detection is mainly dependent on identification of outbreaks by clinicians.

The distinctive feature involves the accumulation of unexplained deaths or instances exhibiting symptoms such as fever and respiratory distress. Casualties are dispersed in time and location; therefore, real-time data from emergency health care facilities might prove essential for effective surveillance. All health care providers, including those in renal care units, should be familiar with the characteristics of exposure to a biological warfare agent as well as with the general principles of its management (Table 3).

The early recognition of a biological warfare event is important in order to apply timely, specific prophylaxis or therapy (i.e., medications, anti-serum, or vaccines). In this context, the categories of biological warfare agents

according to the European Medicines Agency (EMA), as opposed to the CDC categories, take into account exactly the existence of a specific drug treatment or prophylaxis.[5]

Category I: major infectious diseases for which treatment exists, i.e., anthrax, plague, tularaemia, smallpox, viral haemorrhagic fever, botulism, brucellosis, Q fever, glanders, and melioidosis.

Category II: other bacterial infections, for which treatment exists, i.e., Psittacosis, epidemic typhus (*Rickettsia prowazekii*), tuberculosis, shigellosis, salmonellosis, and cholera.

Category III: biological agents for which currently no specific treatment can be recommended, i.e., enterohaemorrhagic *Escherichia coli*, cryptosporidiosis, viral encephalitis (Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis), nipah virus, additional viral haemorrhagic fevers (tick-borne encephalitis virus, yellow fever virus, hantavirus, marburg and ebola virus), staphylococcal enterotoxin B, *Clostridium* perfringens epsilon toxin, ricin toxin.

Clinicians can more effectively plan for prophylaxis and treatment thanks to this categorization, which also includes recommendations for specific medical treatments. The EMA/CHMP guidance document describes in detail the medicinal products used for prophylaxis and treatment of biological warfare agent exposure.[6]

Severe AKI is mostly a late complication of exposure to a biological agent, and biological warfare casualties treated in renal units may be those who have developed multiorgan failure due to septicaemia following biological warfare agent exposure. Supportive measures and specific treatment according to the above-mentioned EMA/CHMP guidance document[6] should be adequately continued in parallel to renal replacement therapy.

Management of biological warfare hazards in Renal Units

Renal units in hospitals that are receiving victims of a biological attack are principally integrated into the management plan of the hospital. Nevertheless, they should have their own emergency plan in order to address specific problems faced in the renal unit (Table 4).

The first step of such an emergency management plan is to consider whether patients on chronic HD, treated in the renal unit should be transferred for treatment in another unit. This decision is based mainly on the capability of the renal unit to treat casualties adequately without putting patients at risk of contamination. Furthermore, the room for treatment of infected patients should be separated from non-infectious patients on acute or even chronic HD. Patients on PD should be advised to avoid routine unit visits until the biological hazard is managed.

Depending on the suspected biological warfare agent, specific precautions are indicated to control the spread of the infection. Renal unit staff that are in contact with infected patients should use personal protective equipment (PPE).[7] Contact, droplet, and airborne transmission precautions are indicated as needed. Self-protection measures are essential, and every health care provider should have received adequate training on these measures.[7-9] In cases of toxin exposure, a rigorous decontamination, similar to that followed in cases of chemical agent exposure, should have already been applied before entry into the renal Unit (see Chapter 4).

The unit's capability should be continually assessed in order to maintain adequate treatment for victims and patients receiving chronic dialysis. Good communication is important as it will ensure up-to date information. For example, the identity and detection method of the biological agent involved are uniquely valuable pieces of information. In this way, adequate medical treatment, including infection control and personal prophylaxis, can be provided.

Toxins from plant or microbial sources are also included among biological agents. Ricin, naturally found in castor beans, for example, is listed as a category B agent and botulinum toxin as a category A agent, according to the CDC. Inhalation of aerosolized or powder formulations or ingestion are the main routes of exposure in these cases. Decontamination and prophylactic measures to avoid the spread of toxin exposure are similar to those used for chemical warfare agents (see Chapter 4).

The staff of the renal unit should be informed about any prophylactic or therapeutic drug administration indicated. The state health official authorities provide information and guidance for clinicians on treatment and prophylaxis in dependence on the specific infection and the available

treatment supplies. Chemoprophylaxis is available for various infections such as anthrax, plague, tularemia, brucellosis, Q fever, glanders, and melioidosis.[10,11]

Polyclonal and monoclonal antibodies are also being developed against toxins (ricin, botulinum toxin, *Bacillus anthacis* toxin) and against anthrax infection (polyclonal).[12] Some vaccines, e.g., against Ebola, anthrax, and smallpox, are also available.[13]

Infections after biological weapon exposure (e.g., anthrax) very often lead to septicaemia and multiorgan failure, which is generally accompanied by an AKI and requires renal replacement therapy. The prevalence of septic shock is enhanced in these cases; therefore, continuous methods of renal replacement therapy -Continuous Veno-Venous Haemofiltration (CVVH), Haemodialysis (CVVHD), or Haemodialfitration (CVVHDF)- are better than Haemodialysis, Haemofiltration, and Haemodiafiltration, which are done on an as-needed basis. Continuous treatment should be applied inside an Intensive Care Unit (ICY) and staff of the HD unit may not be involved or may be only partially involved in treatment. The protocols for self-protection and infection control should be applied according to the essential PPE in the ICU.

Principles of management in massive biological weapons incidents

The renal unit staff, like every other health care professional, should be aware of biological warfare agent exposure and at least familiar with the general measures of its management (Table 3).

Table 3. *General principles of management in an incident of massive exposure to agents of biological warfare*

Principles of management in massive biological weapons incidents
Surveillance, recognition, and containment of outbreaks
Confirmation and detection of new cases (by laboratory methods)
Specific prophylaxis for presumed exposure
Specific therapy for a possible or confirmed disease
Cleanup of hazards and infections and epidemiological study

Hospital renal units should have their own emergency plan for such an incident. In order to avoid an intra-hospital or intra-unit outbreak, the transfer of chronic dialysis patients might be needed. A liaison and a safety officer should be appointed. Self-protection of staff and infection control measures should be rigorous, always in dependence on the specific infection (Table 4).

Table 4*. Specific measures and management applied in Renal Units after a biological weapon exposure*

Renal Units: Management of a biological weapons exposure
Elaborate Renal Unit emergency plan for chemical mass exposure
Define the exact room for the treatment of infected victims
Consider the transfer of dialysis patients for chronic treatment
Appoint a disaster-specific liaison and a safety
Remain fully informed about the causative agent and all management (e.g., prophylaxis and treatment) procedures
Apply rigorous self-protection to staff and infection spread control measures
Consider continuous treatment* in the ICU for AKI with multiorgan failure

*Continuous Veno-Venous Haemofiltration (CVVH), Haemodialysis (CVVHD), or Haemodiafilitration (CVVHDF)

Conclusion

Biological weapons spread rapidly, independent of any national borders. The key point is to diminish contamination and reduce overall morbidity and mortality by early recognition of biological warfare in order to apply timely specific prophylaxis or therapy.

Useful links about Biological Hazards

- Convention on the Prohibition of the Development, Production, Stockpiling and Use of Biological Warfare Weapons (Biological Weapons Convention): https://www.un.org/disarmament/biological-weapons
- European Medicines Agency (EMA): Biological and chemical threats. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/biological-chemical-threats
- Personal Protection Equipment [PPE] defined by the Occupational Safety and Health Administration (OSHA) https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.120AppB.

- Eurosurveillance. Europe's journal on infectious disease surveillance, epidemiology, prevention and control. Full-texts including the term "biological weapons" https://www.eurosurveillance.org/search?value1=biological+weapons&option1=fulltext
- Centers of Disease Control. Anthrax Information for Healthcare Professionals. https://www.cdc.gov/anthrax/healthcare/

References

1. Wheelis M. Investigating Disease Outbreaks under a Protocol to the Biological and Toxin Weapons Convention. *Emerg Infect Dis*. 2000;6(6):595-600. doi.org/10.3201/eid0606.000607
2. Centers for Disease Control and Prevention. Bioterrorism Agents/Diseases, by Category http://emergency.cdc.gov/agent/agentlist-category.asp (accessed on 31st January 2023).
3. Adalja AA, Toner E, Inglesby TV. Clinical management of potential bioterrorism-related conditions. *N Engl J Med*. 2015;372:954-62. doi: 10.1056/NEJMra1409755.
4. European Medicines Agency (EMA): Biological and chemical threats. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/biological-chemical-threats (accessed on 31st January 2023)
5. European Medicines Agency (EMA), Committee on Proprietary Medicinal Products (CPMP). Guidance document on use of medicinal products for treatment and prophylaxis of biological agents that might be used as weapons of bioterrorism. https://www.ema.europa.eu/documents/regulatory-procedural-guideline/european-medicines-agency/committee-proprietary-medicinal-products-guidance-document-use-medicinal-products-treatment_en.pdf
6. Siegel JD, Rhinehart E, Jackson M, Chiarello L. Health Care Infection Control Practices Advisory Committee. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Health Care Settings. *Am J Infect Control.* 2007;35(10 Suppl 2):S65-164. doi: 10.1016/j.ajic.2007.10.007.
7. Singh VV, Mannan Boopathi, Thakare VB, Thavaselvam D, Singh B. Protective equipment for protection against biological warfare agents. In (eds.) Flora SJS, Pachauri V. Handbook on Biological Warfare Preparedness. Cambridge, Massachusetts, US. Academic Press; 2020: pp 173-194. doi.org/10.1016/B978-0-12-812026-2.00009-8
8. Inglesby TV, Dennis DT, Henderson DA, Bartlett JG, Ascher MS, Eitzen E, Fine AD, Friedlander AM, Hauer J, Koerner JF, Layton M, McDade J, Osterholm MT, O'Toole T, Parker G, Perl TM, Russell PK, Schoch-Spana M, Tonat K. Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA*. 2000;283(17):2281-90. doi: 10.1001/jama.283.17.2281.
9. Russell P, Eley SM, Bell DL, Manchee RJ, Titball RW. Doxycycline or ciprofloxacin prophylaxis and therapy against experimental Yersinia pestis infection in mice. *J Antimicrob Chemother*. 1996;37(4):769-74. doi: 10.1093/jac/37.4.769.
10. Russell P, Eley SM, Ellis J, Green M, Bell DL, Kenny DJ, Titball RW. Comparison of efficacy of ciprofloxacin and doxycycline against experimental melioidosis and glanders. *J Antimicrob Chemother.* 2000;45(6):813-8. doi: 10.1093/jac/45.6.813.
11. Rainey GJ, Young JA. Antitoxins: novel strategies to target agents of bioterrorism. *Nat Rev Microbiol*. 2004;2(9):721-6. doi: 10.1038/nrmicro977.
12. Garner JS. Guideline for isolation precautions in hospitals. The Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol*. 1996;17(1):53-80. doi: 10.1086/647190.

ISBN 978-618-86506-9-5