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ABOUT JOURNAL

Aim and scope

Annales Medicinae Urgentis (AMU) is a open-access peer reviewed medical journal published by the Croatian Society for Emergency Medicine that aims to improve the care of patients with emergency and critical illness by acquiring, discussing, distributing, and promoting evidence-based information relevant to emergency physicians and intensivists.

It publishes original original articles, reviews, case reports, meta-analysis, comments, methodologies, perspectives/ viewpoints, editorials, images, news, communications, letters to the editor, etc with no restrictions on the maximum length of manuscripts, provided that the text is concise and comprehensive. The AMU uses the Diamond Open Access model. This means that there are NO author processing fees and no fees to access the published papers.

HLZ - HRVATSKO DRUŠTVO ZA HITNU MEDICINU
CMA - CROATIAN SOCIETY OF EMERGENCY MEDICINE

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ANNALES MEDICINAE URGENTIS: *MESSAGE FROM THE EDITORS*

Prof. Višnja Nesek Adam, MD, PhD

Prof. Ivan Gornik, MD, PhD

Dear Colleagues,

With great excitement and gratitude, we announce the release of the second issue of Annales Medicinae Urgentis, the official open-access, peer-reviewed journal of the Croatian Medical Association - Croatian Society of Emergency Medicine (CMA - CSEM). As the editors, we are proud to continue this important project, which marks a significant step in the ongoing development of our Society and the field of emergency and critical care medicine.

This issue is especially enriched by works from young physicians awarded for the best poster presentations at the 9th Symposium in Rijeka, highlighting the promising future of emergency medicine in Croatia.

This journal is the natural continuation of our collective efforts to improve patient care in emergency and critical situations. By providing a platform for sharing evidence-based knowledge, clinical experiences, and innovative ideas, Annales Medicinae Urgentis serves as a space where emergency physicians, intensivists, and healthcare professionals from diverse disciplines can come together to learn, collaborate, and grow.

Our mission is to create a journal that reflects the best of our profession, one that promotes the exchange of ideas, encourages scientific discussion, and fosters a community of practice that will ultimately improve patient outcomes. We aim to publish a wide variety of articles, including original research, reviews, case reports, meta-analyses, editorials, and more. We are committed to maintaining high scientific standards while keeping the journal accessible and relevant to all healthcare professionals working in emergency and intensive care settings.

We strongly believe that Annales Medicinae Urgentis can grow into a respected and essential publication, but this will only happen with your active support. We encourage you to submit your work, share your expertise, and help us build this journal into a meaningful resource for our profession.

We thank all contributors—authors for their dedication and trust, and reviewers for their invaluable feedback, which ensures the quality and integrity of each issue.

Looking ahead, we are excited about the future of Annales Medicinae Urgentis. We will continue expanding our editorial team and collaborations to grow both content and impact. Our ultimate goal is indexing and international recognition, and with your support, we are confident this will be achieved.

Launching and nurturing this journal is a big step forward for the Croatian Society of Emergency Medicine. Together, we can build Annales Medicinae Urgentis into a recognized and valued resource that advances emergency and critical care medicine.

Thank you for your trust and belief in this project.

Warm regards,

Prof. Višnja Nesek Adam, MD, PhD
and *Prof. Ivan Gornik, MD,PhD*
Editors-in-Chief, Annales Medicinae Urgentis

REVIEW ARTICLE / PREGLEDNI ČLANAK

CURRENT MANAGEMENT OF ATRIAL FIBRILLATION IN THE EMERGENCY DEPARTMENT

ZBRINJAVANJE ATRIJSKE FIBRILACIJE U HITNOM BOLNIČKOM PRIJEMU

***Murat Ersel**[1]

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Abstract

Atrial fibrillation is the most common type of arrhythmia diagnosed in the emergency department. Many patients are diagnosed with new-onset atrial fibrillation in the emergency department. The 2024 European Society of Cardiology guidelines (ESC) introduce a new approach for management of atrial fibrillation called as AF-CARE.

While atrial fibrillation with rapid ventricular response disrupts the hemodynamic status of the patient or rate control is an important problem to be solved acutely in emergency departments, also early and accurate diagnosis, selection of appropriate rate and rhythm control agents and identification of patients in need of anticoagulation will be important milestones for the management of atrial fibrillation in the emergency departments to better prevent important complications such as stroke and heart failure. Nowadays, emergency physicians also play an important role not only in the proper management of atrial fibrillation in the emergency department but also in initiating a teamwork based management as recommended in the AF-CARE approach.

Keywords: atrial fibrillation; emergency department; acute care; rhythm control; anticoagulation

Sažetak

Atrijska fibrilacija najčešća je vrsta aritmije dijagnosticirana u hitnom bolničkom prijemu. Mnogi bolesnici prvi put budu dijagnosticirani s novonastalom atrijskom fibrilacijom upravo u hitnom prijemu. Smjernice europskog društva za kardiologiju (engl. *European Society of Cardiology guidelines, ESC)* iz 2024. godine uvode novi pristup u zbrinjavanju atrijske fibrilacije, nazvan **AF-CARE**.

Atrijska fibrilacija s brzim ventrikularnim odgovorom može narušiti hemodinamsku stabilnost bolesnika, a kontrola frekvencije često je hitan terapijski izazov u hitnoj službi. Rana i točna dijagnoza, odabir odgovarajućih lijekova za kontrolu frekvencije i ritma, te pravovremena identifikacija bolesnika kojima je potrebna antikoagulacijska terapija predstavljaju ključne korake u zbrinjavanju atrijske fibrilacije u hitnoj službi s ciljem prevencije ozbiljnih komplikacija poput moždanog udara i srčanog zatajenja. Danas liječnici hitne medicine imaju važnu ulogu ne samo u pravilnom zbrinjavanju atrijske fibrilacije, već i u pokretanju timskog pristupa liječenju, kao što preporučuje pristup **AF-CARE**.

Ključne riječi: atrijska fibrilacija; hitna služba; akutna skrb; kontrola ritma; antikoagulacija

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Introduction

Atrial fibrillation (AF), is the most diagnosed arrythmia in the emergency departments EDs. It affects an estimated 60 million people worldwide and significantly contributes morbidity and mortality (1–3). The prevalence of atrial fibrillation is expected to increase in future due to aging population, rising number of comorbidities, greater awareness, and advances in detection technologies. In 2060, the prevalence of AF is expected to double compared to 2010. The lifetime risk of developing AF will increase from 1 in 5 to 1 in 3, and health expenditures related to AF will rise from 1 % to 2 % of total healthcare spending (4). Due to the anticipated increase in patient visits, a rise in the burden on emergency departments is expected.

Many patients visit EDs as a first point of care with acute symptoms. These symptoms may even minor symptoms, including palpitations, dizziness, which makes it challenging to establish a diagnostic correlation with atrial fibrillation initially. Some patients are referred to the ED with more severe complaints, like chest pain or complications, such as thromboembolism or exacerbation of heart failure (5,6).

Atrial fibrillation increases the risk of stroke, heart failure, and death, with around 70 % of cases requiring hospitalization.

AF raises stroke risk five-fold, heart failure three-fold, and mortality two-fold, placing a substantial burden on healthcare systems, especially EDs (7,8). About 70 % of ED visits for AF is resulting with hospitalization (9). Atrial fibrillation is often linked to ischemic or valvular heart disease, while less common causes include congestive cardiomyopathy, myocardytis, binge drinking ("holiday heart"), thyrotoxicosis, and blunt chest trauma (10,11). Admissions due to atrial fibrillation are quite common in the emergency department. Approximately 1–2 % of the ED visits are due to AF (12). Emergency physicians should keep in mind that more then 50 % percent of paroxysmal AF spontaneously revert to sinus rhythm with in 8-16 hours, only about a 1/3 of the patients seek for ED care after onset. (13,14).

Emergency physicians, play a pivotal role in early management, to detect and recognise atrial fibrillation, manage its complications, and plan the anticoagulation therapy. Their aprroaches may effect both acute and long-term prognosis of the patient, yet AF management approaches vary widely, influenced by resources, cardiology access, and patient characteristics (15). Effective management efforts made in the ED's in every step from early detection to proper treatment will help reduce the risk of future complications. Early diagnosis of symptomatic and asymptomatic AF is important to improve the patient's prognosis in the future, also initiation of early treatment can reduce the occurrence of heart failure and stroke (16). In this review, we would like to discuss the management of patients presenting with atrial fibrillation or atrial fibrillation with other complaints in the ED.

Definition and Classification of atrial fibrillation

Atrial fibrillation is a type of supraventricular arrhythmia characterized by uncoordinated activation of the atria, leading to a loss of effective atrial contraction. On an electrocardiogram (ECG), AF is indicated by the absence of distinct and regular P waves, along with irregular ventricular activation. This results in no specific pattern in the RR intervals, provided there is no atrioventricular block present (4).

It is important to recognize that various types of AF can be observed during visits to the emergency department according to their temporal pattern (Table 1). Note that these categories reflect observed episodes of AF and do not imply the underlying pathophysiological process. Additionally, there are cases where the patient is not experiencing atrial fibrillation at the time of the ED visit, including paroxysmal AF or permanent AF. First diagnosed atrial fibrillation is a form of AF that has not previously been diagnosed, regardless of symptoms, temporal pattern, or duration.(4)

Table 1. Definitions and classifications for the temporal pattern of atrial fibrilation

Temporal Classification	Definition
First-diagnosed AF	AF that has not been diagnosed before, regardless of symptom status, temporal pattern, or duration.
Paroxysmal AF	AF which terminates spontaneously within 7 days or with the assistance of an intervention. Evidence suggests that most self-terminating paroxysms last <48 h.
Persistent AF	AF episodes which are not self-terminating. Many intervention trials have used 7 days as a cut-off for defining persistent AF. Long-standing persistent AF is arbitrarily defined as continuous AF of at least 12 months' duration but where rhythm control is still a treatment option in selected patients, distinguishing it from permanent AF.
Permanent AF	AF for which no further attempts at restoration of sinus rhythm are planned, after a shared decision between the patient and physician.

AF - atrial fibrillation

Table 2. Other clinical concepts relevant to atrial fibrillation

Clinical Concept	Definiton
Clinical AF	Symptomatic or asymptomatic AF that is clearly documented by an ECG (12-lead ECG or other ECG devices). The minimum duration to establish the diagnosis of clinical AF for ambulatory ECG is not clear and depends on the clinical context. Periods of 30 s or more may indicate clinical concern, and trigger further monitoring or risk stratification for thromboembolism.
Device-detected subclinical AF	Device-detected subclinical AF refers to asymptomatic episodes of AF detected on continuous monitoring devices. Confirmation is needed by a competent professional reviewing intracardiac electrograms or an ECG-recorded rhythm. Device-detected subclinical AF is a predictor of future clinical AF.
AF burden	The overall time spent in AF during a clearly specified and reported period of monitoring, expressed as a percentage of time.
Recent-onset AF	There is accumulating data on the value of the term recent-onset AF in decision-making for acute pharmacological or electrical cardioversion of AF. The cut-off time interval to define this entity has not yet been established.
Trigger-induced AF	New AF episode in close proximity to a precipitating and potentially reversible factor.
Self-terminating AF	Paroxysmal AF which terminates spontaneously. This definition may be of value for decisions on acute rhythm control taken jointly by the patient and healthcare provider.

AF- atrial fibrillation; ECG - electrogadiogram

In first-diagnosed atrial fibrillation, it is crucial to assess whether the condition is reversible and to implement the necessary protocols for suitable patients. Additionally, it is advisable to initiate anticoagulation early for patients with a CHA_2DS_2-VASc score above the recommended threshold after newly diagnosed atrial fibrillation is identified in the emergency department (4). It is important to note that these categories reflect observed episodes of AF and do not imply the underlying pathophysiological process.

There are another terms and definitions of the AF related to the type and the way it is presented. On Table 2. is examples of current terminology given.

Also AF may classified by the way it presents, the term "valvular atrial fibrillation" refers to patients with valvular pathologies, such as severe or moderate mitral stenosis (17). AF can also be classified according to its presentation. For instance, if it is mostly asymptomatic and only becomes apparent when a thromboembolic event is diagnosed through a routine ECG conducted for other purposes, it is defined as subclinical or occult AF (18).

Conversion to sinus rhythm increases the risk of thromboembolic events, especially within the first 10 days, requiring anticoagulation in high-risk patients.

Another term that has fallen out of favor is "lone AF". This term referred to the first episode of AF diagnosed in younger patients (under 60 years) with paroxysmal, persistent, or permanent AF who do not have structural heart disease or significant cardiovascular risk factors. These patients are classified with "0" points on the CHA_2DS_2-VAS score, indicating the lowest risk for thromboembolic events associated with AF (18,19).

The conversion to sinus rhythm, whether achieved electrically, pharmacologically, or spontaneously, is associated with an incremental increase in the risk of thromboembolic events for patients due to more depressed atrial function. Most of the thromboembolic events occur within 10 days after conversion to the sinus rhythm (20). Therefore for high risk patients according to the CHA_2DS_2-VA score should be anticoagulated.

Clinical Presentation

Symptoms

AF patients may experience a range of symptoms, including palpitations, shortness of breath, fatigue, chest pain, dizziness, poor exercise capacity, fainting, anxiety, depression, and disrupted sleep (4). The key issue is early recognition an awareness of the atrial fibrilation-associated symptoms in patients who have no knowledge of existing atrial fibrillation. It is crucial for emergency physicians to consider atrial fibrillation in the differential diagnosis when evaluating patients presenting to the ED with symptoms potentially related to AF, and to obtain an electrocardiogram promptly.

Another key consideration ascertain any underlying cause of a newly detected AF and conduct a complete review of the patient's past medical history and current medication regimen. This approach will provide a critical information to assist in determining the most appropriate therapeutic strategy for treating the patient in the ED and the subsequent need for hospital admission (9). These

underlying conditions may be heart failure, pulmonary embolism, or volume overload. Symptoms associated with AF are not only typical palipatitons, they are variable and broad (Table 3). More importantly, many episodes of AF even among symptomatic patients, may present asymptomaticaly (21). However, the presence or absence of symptoms does not correlate with the incidence of stroke, systemic embolism, or mortality (21), but symptoms decrease the quality of life of a patient (22,23).

Emergency physicians must promptly recognize AF symptoms and perform an ECG to accurately diagnose AF and identify underlying causes for appropriate treatment.

Table 3. Patient symptoms associated with atrial fibrilation

Palpitations	Chest pain
Shortness of breath	Dizziness
Fatigue	Poor exercise capacity
Fainting (syncope)	Anxiety
Depressed mood	Disordered sleep

Complications of atrial fibrilation

AF increases the risk of heart failure 4-5 fold (24,25), stroke 2-3 fold ischemic heart diseases about a 2 fold as well (25–27). AF is also linked to cognitive impairment and vascular dementia, depression, increased hospitalization recurrence, thromboembolic events, impaired quality of life and increased risk of death (4).

The primary cause of death is heart failure (26) compared to sinus rhythm, also bleeding risk increases in AF patients who are on oral anticoagulants (OACs) therapy (4).

Diagnostic Evaluation of atrial fibrilation in the Emergency department

A detailed medical history should be obtained from all patients with AF in the ED and, also comphrensive diagnostic work-up should be applied. Medical history helps to determine the pattern of AF, comorbidities, relevant family history and assess the risk factors for thromboembolism and bleeding (4).

For patients with newly diagnosed AF or suspected arrhythmia, initial evaluation should include assessment of comorbidities and risk factors, along with 12-lead ECG monitoring. The ECG should confirm the rhythm, determine ventricular rate, and detect any conduction abnormalities (28).

Additionally, liver and kidney functions, electrolyte levels, and risks of stroke, coronary artery disease, and bleeding risk should be assessed using N-terminal pro-brain natriuretic peptide (NT-proBNP), troponin, complete blood count, blood glucose, and if possible thyroid function tests. HbA1c should be requested for further evaluation (29,30). According to the multidisciplinary AF management principles summarized under AF-CARE, transthoracic echocardiography (TTE) is recommended in the emergency department to guide treatment planning. However, in settings with limited access to TTE, initiation of oral anticoagulation and adherence to guideline-recommended strategies should not be delayed (4).

AF – CARE Approach to the atrial fibrilation management

The ESC 2024 Guidelines place the AF-CARE principles at the core of atrial fibrillation management (Table 4). This patient-centered, multidisciplinary approach to AF management is a care model that respects patients' experiences, values, needs, and preferences in the planning, coordination, and delivery of care. It integrates all aspects of management, including symptom control, comorbidity management, psychosocial support, lifestyle recommendations, and the selection of optimal medical treatment options. The restructuring into AF-CARE reflects recent developments in new approaches and technologies, particularly concerning rhythm control. Evidence increasingly shows that managing AF is more effective when comorbidities and risk factors are considered (4).

AF-CARE offers multidisciplinary, patient-centered care combining symptom control, comorbidity management, psychosocial support, lifestyle changes, and optimal treatment to enhance atrial fibrillation management.

A careful search for comorbidities and risk factors [C] is essential for all patients diagnosed with atrial fibrillation. The next step is to focus on preventing stroke and thromboembolism [A] in patients with identified risk factors, which involves the appropriate use of anticoagulant therapy. Following this, efforts should be directed toward reducing AF-related symptoms and morbidity through effective heart rate and rhythm control [R]. In selected patients, this approach may also lead to decreased hospitalization rates and improved prognosis. The potential benefits of rhythm control should be carefully evaluated for all patients during each healthcare interaction, considering all associated risks. Since AF and its related comorbidities can change over time, it is important to employ various levels of evaluation [E] and re-evaluation for each patient, ensuring that these approaches remain dynamic and adaptable (4).

Table 4. Patient-centered AF – CARE management

Components of Patient-Centered AF Management	How To Implement Patient-Centered AF Management
Optimal treatment according to the AF-CARE pathway, which includes:	Shared decision-making
° [C] Comorbidity and risk factor management	Multidisciplinary team approach
° [A] Avoid stroke and thromboembolism	Patient education and empowerment, with emphasis on self-care
° [R] Reduce symptoms by rate and rhythm control	Structured educational programmes for healthcare professionals
° [E] Evaluation and dynamic reassessment	Technology support (e-Health, m-Health, telemedicine)*
Lifestyle recommendations	
Psychosocial support	
Education and awareness for patients, family members, and caregivers	
Seamless co-ordination between primary care and specialized AF care	

* e-Health refers to healthcare services provided using electronic methods; m-Health refers to healthcare services supported by mobile devices; and telemedicine refers to remote diagnosis or treatment supported by telecommunications technology.

Patient Management
The Unstable Patient

Assessing the stability of patients with atrial fibrillation is a fundamental aspect of AF management in the ED. For patients with recent-onset AF and a rapid ventricular response that is producing hypotension, myocardial ischemia, or pulmonary edema, treat with urgent electrical cardioversion (31,32).

However, instability may not be the only factor caused due to rapid ventricular response tachycardia or hypotension. Various underlying causes can lead to this condition, including sepsis, myocardial infarction, gastrointestinal bleeding, alcohol withdrawal, pulmonary embolism, and metabolic disorders (such as hyperthyroidism or diabetic emergencies). Effective management requires addressing these underlying factors, which may involve interventions aimed at controlling the heart rate or rhythm (33).

Patients with hemodynamic instability due to rapid AF that does not respond to medication, or those contraindicated, such as patients with Wolff-Parkinson-White syndrome, may require immediate restoration of sinus rhythm. In these cases, restoration of sinus rhythm takes precedence over preventing thromboembolic complications. Electrical cardioversion is generally a safe and effective procedure, often with fewer side effects, and it is appropriate also for patients who have structural or functional heart disease (31). However, there are risks associated with the procedure, including complications related to sedation, such as hypotension and respiratory depression. Additionally, patients often experience significant anxiety before the procedure due to concerns about the electrical shock involved (24,25).

Of course, the main risk in the case of an urgent cardioversion is thromboembolic advers events. To reduce the risks associated with left atrial appendage stunning, emergency cardioversion should be preceded as soon as possible by anticoagulation, which can include low-molecular-weight heparin (LMWH) or a bolus of unfractionated heparin. Unless contraindicated, anticoagulation should continue for four weeks following cardioversion (31,34). Cardioversion with using defibrillators that deliver biphasic waveforms are recommended. Their efficacy is higher than monophasic defibrillators, in terms of sinus rhythm restoration (94 vs 84 %) and total energy needed was lower to restore the sinus rhythm (35,36). The use of biphasic waveforms may be of particular benefit in patients who fail to revert with the use of monophasic waveforms (37).

The 2014 American Heart Association (AHA) guidelines do not provide a clear recommendation for a specific energy level for cardioversion and defibrillation in the management of atrial fibrillation. Therefore, it may be advisable to follow the recommendations from the 2010 AHA guidelines. According to these guidelines, the initial energy level for cardioversion of AF should be at least 120 joules when using biphasic defibrillators. This energy level can be increased to a maximum of 200 joules. For atrial flutter, the guidelines recommend lower energy levels, typically between 50 to 100 joules (18,38).

Electrical cardioversion with anticoagulation is essential for unstable AF patients to restore sinus rhythm safely and reduce thromboembolic risk.

In the ED, patients at an increased risk of stroke who require electrical or pharmacological cardioversion should receive anticoagulation either before or immediately after the procedure. This can be accomplished with intravenous heparin, low molecular weight heparin (LMWH), oral factor Xa inhibitors (such as rivaroxaban or apixaban), or oral direct thrombin inhibitors (DOAC) (like dabigatran). Furthermore, high-risk stroke patients should continue long-term anticoagulation for at least four weeks after normal sinus rhythm is restored (39).

According to the recommendation of the UpToDate, if a cardioversion needs to be applied in 3 hours, physicians may begin the anticoagulation with starting intravenous unfractionated heparin (bolus and continuous drip goal partial thromboplastin time 1.5 to 2.0 times control) or a low molecular weight heparin (1 mg/kg subcutaneously every 12 hours). To give heparin and DOAC together is not recommended, if warfarin is selected for anticoagulation, the therapy will continued with both warfarin and heparin until the were the INR exceed 2.0. (34).

Rhythm versus Rate control current recommendations

After ensuring the patient's hemodynamic stability and symptom control, the second step should be the decision for choosing the rate or rhythm control strategy, and thereafter protection of the patient from the thromboembolic events (4). To choose the rate or rhythm control-based strategy some factors should be assessed. Another issue is to clear the AF initiation time, is this a recent-onset (within 24 hours) or persistent (over 24 hours) AF.

The latest 2024 ESC Guidelines suggest that electrical cardioversion (ECV) is generally feasible and highly effective, especially for patients who present within the "safe window" of less than 24 hours after the onset of atrial fibrillation in the emergency department. In this patient group, it is important to have trained personnel and sedation anesthesia support for the effective application of electrical cardioversion. For patients with AF lasting longer than 24 hours or when the onset time is unknown, adequate anticoagulation or transesophageal echocardiography may be necessary to rule out the presence of a left atrial thrombus, which could delay the procedure (4).

Rate vs. rhythm control depends on AF duration, stability, and risks; electrical cardioversion is preferred within 24 hours or for unstable patients.

Some studies suggest that rate control may be a safer initial option for stable AF patients, while others advocate for rhythm control as a means of potentially improving long-term outcomes, particularly in younger, symptomatic patients (4,16,39).

In the ED, in patients with hemodynamic instability or suffering from severe symptoms, in younger patients, and in cases of recent-onset AF (within 24 hours) to choose the rhythm control strategy may be reasonable. In older patients, patients with heart failure or previously experienced thromboembolic events, the rate control strategy has to be chosen (15).

Electrical cardioversion also should be considered, as urgent in pre-excitation syndromes, such as AF with Wolff-Parkinson-White syndrome, where irregular conduction through accessory pathways can lead to ventricular fibrillation. Additionally, ECV is often the next therapeutic option for patients with severe symptomatic AF that is unresponsive to pharmacological treatments (15).

Rate control

Rate control is traditionally preferred in the ED for stable AF patients, as it involves straightforward and low-risk management with medications (40,41). These medications are used to manage heart rate, which is crucial for reducing symptoms and preventing complications associated with atrial fibrillation.

The AFFIRM trial (42) suggested a target heart rate of less than 110 beats per minute (bpm) for patients with persistent or permanent AF, as this was associated with satisfactory outcomes without an increase in adverse events. However, there is no clear consensus on the optimal target heart rate during acute presentations in the emergency department (ED). This underscores the need for further research, particularly to assess how heart rate management impacts long-term outcomes for patients in this group (43,44).

Before initiating rate or rhythm control therapy, underlying causes should be evaluated, which include treatment of reversible causes such as sepsis, volume overload and cardiogenic shock. The treatment strategy should be designed according to the patient's characteristics, presence of heart failure and LVEF, and haemodynamic profile (4).

For acute rate control in AF, beta-blockers are generally recommended across all levels of left ventricular ejection fraction (LVEF), while non-dihydropyridine calcium channel blockers such as diltiazem and verapamil are preferred in patients with LVEF >40 %. These agents are favored over digoxin due to their more rapid onset of action and dose-dependent pharmacodynamics (45–47). Selective beta-1 adrenergic receptor blockers have greater efficacy and a better safety profile than non-selective beta-blockers (48). In certain acute situations, combination therapy with digoxin may be necessary; however, the concurrent use of beta-blockers alongside diltiazem or verapamil should be avoided unless under strict clinical supervision due to the potential for adverse hemodynamic interactions (49,50). In patients who are hemodynamically unstable or have a severely reduced LVEF, intravenous agents such

as amiodarone, landiolol, or digoxin may be considered appropriate therapeutic alternatives (4).

Rhythm control

In the ED, electrical conversion of rhythm is generally feasible and highly effective, especially for patients presenting within the "safe window" of less than 24 hours from the onset of atrial fibrillation, where the risk of thromboembolism is relatively low, as indicated by the 2024 ESC guidelines (4).

The time limit for any thromboembolic event may called as "safe window", decrased from 48 to 24 hours in 2024 ESC guidelines. However, the exact onset of AF is often unknown, and observational studies indicate that the risk of stroke or thromboembolism is lowest within a much shorter timeframe (51–53).

Rhythm control is a viable option for patients who have a longer life expectancy and those whose atrial fibrillation onset occurred less than 24 hours before presentation. This approach is suitable for patients who have been anticoagulated for 3 to 4 weeks or who undergo transesophageal echocardiography that shows no intracardiac thrombus. Direct oral anticoagulants are considered a safe and reliable choice for anticoagulation (33).

For the hemodynamically stable patients with recent-onset AF, a wait-and-see approach may be a viable alternative to immediate cardioversion. The Rate Control versus Electrical Cardioversion Trial 7—Acute Cardioversion versus Wait-and-See (RACE 7 ACWAS) studied patients with recent-onset symptomatic atrial fibrillation who did not have hemodynamic compromise. The trial found that allowing time for spontaneous conversion up to 48 hours after the onset of AF symptoms was non-inferior to immediate cardioversion when assessed at a 4-week follow-up (4,54).

Also, cardioversion is generally not recommended if AF has persisted for more than 24 hours, unless the patient has received at least 3 weeks of therapeutic anticoagulation or a transoesophageal echocardiogram (TOE) performed, which confirms the absence of intracardiac thrombus (4,54–56).

Following cardioversion, oral anticoagulation should be continued for a minimum of 4 weeks in most cases. OAC may be omitted only in patients without thromboembolic risk factors and with sinus rhythm restored within 24 hours of AF onset. However, if any thromboembolic risk factors are present, long-term OAC is indicated regardless of rhythm outcome (4).

Another challenging question to answer about AF management in the ED is the decision about rhythm control after admission to the ED. Most current guidelines provide more cautious recommendations to reduce the risk of a possible thromboembolic event. Even in older studies it have shown to institute when compared with rate control strategies, rhythm control strategy using anti-arrhythmic drugs does not reduce the mortality and morbidity, in contrast to findings of recent strategies have shown that rhythm control strategy increase quality of life once sinus rhythm is maintained (57,58).

At that point, evidence specific to the emergency department setting is still insufficient to determine how atrial fibrillation impacts patient outcomes. It remains unclear in which patients AF management may lead to decreased readmission rates, improved quality of life, and better long-term recurrence rates. These aspects are still unclear in the management of ED patients with AF (15).

Pharmacologic cardioversion

Pharmacological cardioversion to restore sinus rhythm is an elective procedure for haemodynamically stable patients. It is less effective than ECV for restoring sinus rhythm, with the timing of the cardioversion being a significant factor in its success (59,60). The data is limited on the true efficacy of this procedure, which are likely biased by the spontaneous restoration of sinus rhythm in 76 % – 83 % of patients with recent-onset AF (4).

Within 4 hours, intravenous (IV) vernakalant and flecainide have the highest conversion rates. This may allow to discharge of patients from the ED with sinus conversion to sinus rhythm and decrease the rate of hospitalization. Class IC antiarrhythmics in both IV and oral forms of vernakalant and flecainide superior conversion rates within 12 hours, with flecainide outperforming propafenone. In contrast, amiodarone's efficacy is demonstrated more slowly, typically within 24 hours (61).

The adventage of pharmacological cardioversion is that this treatment does not require fasting, sedation, or anaesthesia. But, anticoagulation should be started or continued according to a formal (re-)assessment of thromboembolic risk. However in all types of pharmacological cardioversion, the drug selection should be made as tailor fit, based on the patients type and severity of concomitant heart disease (4).

Pharmacological cardioversion with vernakalant or flecainide is effective and safer for stable recent-onset AF patients, enabling fast rhythm restoration without sedation but needs careful selection.

In the use of cardioversion of recent-onset AF cases, flecainide and propafenone should be chosen, excluding patients with severe left ventricular hypertrophy, heart failure with reduced ejection fraction (HFrEF), or coronary artery disease. When to use vernakalant for the same procedure, patients with recent ACS, HFrEF, or severe aortic stenosis should be excluded. Cardioversion of AF with IV amiodarone is recommended in patients with severe left ventricular hypertrophy, HFrEF, or coronary artery disease, a delay should be acceptted.

A single self-administered oral dose of flecainide or propafenone (commonly referred to as the "pill-in-the-pocket" approach) is effective for symptomatic patients who experience infrequent and recent-onset paroxysmal atrial fibrillation. To safely implement this strategy, it is essential to screen patients to rule out any conditions such as sinus node dysfunction, atrioventricular conduction defects, or Brugada syndrome. Additionally, prior in-hospital validation of the efficacy and safety of this treatment is necessary (62). An atrioventricular node-blocking drug should be instituted in patients treated with Class IC AADs to avoid 1:1 conduction if the rhythm transforms to atrial flutter (AFL) (63).

Pharmacological cardioversion is not recommended for patients with sinus node dysfunction, atrioventricular conduction disturbances, or prolonged QTc (>500 ms), unless risks for proarrhythmia and bradycardia have been considered (4).

Especially, in cases of recent-onset AF, newer antiarrhythmic drugs, such as vernakalant and dronedarone, offer potential advantages over traditional antiarrhythmics by promoting faster cardioversion with a lower incidence of adverse effects. Vernakalant, for instance, has demonstrated higher efficacy in achieving sinus rhythm compared to ibutilide, as shown in studies like that by Simon et al (64,65).

This rapid, actionable safety profile makes vernakalant a promising choice for ED-based cardioversion, particularly in patients who require urgent rhythm control (66). Despite these benefits, the use of novel antiarrhythmics in the ED remains limited. Concerns about real-world efficacy, cost, and the potential for side effects in high-risk populations contribute to reluctance in their routine adoption (15).

Direct oral anticoagulant initiation and anticoagulation planning

DOACs have significantly improved stroke prevention in atrial fibrillation. They offer a safer bleeding risk profile and eliminate the need for INR monitoring (67). The updated ESC 2024 guidelines now recommend initiating DOAC therapy as early as the ED phase for eligible atrial fibrillation patients, especially those at high risk of stroke (4). However, initiating anticoagulation remains complex for many emergency physicians, who must balance the risk of a thromboembolic event against the risk of bleeding, especially in the absence of guaranteed outpatient follow-up (15). Emergency physicians hesitate, to initiate DOAC therapy due to concerns about continuity of care and anticoagulation monitoring after discharge, particularly for patients with inconsistent access to outpatient follow-up (4,15).

Lack of universally standardized protocols for DOAC initiation in the ED setting contributes to variability in practice (15). Personalized medicine approaches and a multidisciplinary model for care are promising changes in the ED's are being applied now, such as mulidisciplinary teams and AF observation units (31,41,68).

Every patient with atrial fibrillation should be assessed to determine the necessity of antithrombotic therapy for preventing systemic embolization, even during their first episode of AF. Patients diagnosed with AF in the ED, who are not on appropriate anticoagulant medication, should be assessed using the VAS_2DS_2-VA score, as recommended by the latest 2024 guidelines of ESC. This scoring system is a widely used version of the CHA_2DS_2-VAS score, excluding the gender parameter (Table 6) (ESC 2024). A score of 2 or higher is an indication of an increased risk of thromboembolism, which informs the decision to initiate oral anticoagulation therapy (4).

The ESC 2024 guidelines emphasize this approach, particularly for patients presenting with AF within 24 hours, where immediate anticoagulation can significantly reduce the risk of thromboembolic events. Cardioversion is not recommended if AF has persisted for more than 24 hours, unless the patient has received at least 3 weeks of therapeutic anticoagulation (adherence DOAC or INR ≥2.0 for VKA) or a transoesohageal echocardiography has been performed to rule out intracardiac thrombus. After cardioversion, most patients should continue an OAC for at least 4 weeks post-cardioversion (55,56,69).

Also, most patients should continue OAC for at least 4 weeks post-cardioversion, even if CHA_2DS_2-VA = 0, only for those without thromboembolic risk factors and sinus rhythm restoration within 24 h of AF onset is post-cardioversion OAC optional. In patients with thromboembolic risk factor(s) irrespective of whether sinus rhythm is achieved after cardioversion, the OAC should be continued at least 4 weeks to prevent thromboembolism (42,55,56,70).

A CHA_2DS_2-VA score ≥ 2 is recommended as an indicator of elevated thromboembolic risk for decisions on initiating oral anticoagulation(4). In previous guidelines of AHA/ACC 2014, in patients with score of 1, the choice was left to the patients choice based on the clinicians recommends to choose anticoagulation, aspirin, or no anticoagulation. Also ESC was in recommendation for anticoagulation of any patient with a CHA_2DS_2-VASc score of ≥1 for men and ≥2 for women. Now according to latest guidelines of ESC 2024, A CHA_2DS_2-VA score of 1 should be considered an indicator of elevated thromboembolic risk for decisions on initiating oral anticoagulation, with following a patient-centred and shared care approach (4).

Also, oral anticoagulation is recommended in all patients with AF and hypertrophic cardiomyopathy or cardiac amyloidosis, regardless of CHA_2DS_2-VA score, to prevent ischaemic stroke and thromboembolism (4).

In ESC 2024 guidelines, stated that data are lacking on how to treat patients with low risk of stroke (with a CHA_2DS_2-VA score of 0 or 1), as these patients were excluded from large RCTs, and there is no recommendation for patients

Table 6. Updated definitions for the CHA_2DS_2-VA Score

CHA_2DS_2-VA component	Definition and comments	Points awarded
C Chronic heart failure	Symptoms and signs of heart failure (irrespective of LVEF, thus including HFpEF, HFmrEF, and HFrEF), or the presence of asymptomatic LVEF ≤40 %.	1
H Hypertension	Resting blood pressure >140/90 mmHg on at least two occasions, or current antihypertensive treatment. The optimal BP target associated with lowest risk of major cardiovascular events is 120–129/70–79 mmHg (or keep as low as reasonably achievable).	1
A Age 75 years or above	Age is an independent determinant of ischaemic stroke risk. Age-related risk is a continuum, but for reasons of practicality, two points are given for age ≥75 years.	2
D Diabetes mellitus	Diabetes mellitus (type 1 or type 2), as defined by currently accepted criteria, or treatment with glucose lowering therapy.	1
S Prior stroke, TIA, or arterial thromboembolism	Previous thromboembolism is associated with highly elevated risk of recurrence and therefore weighted 2 points.	2
V Vascular disease	Coronary artery disease, including prior myocardial infarction, angina, history of coronary revascularization (surgical or percutaneous), and significant CAD on angiography or cardiac imaging. OR Peripheral vascular disease, including: intermittent claudication, previous revascularization for PVD, percutaneous or surgical intervention on the abdominal aorta, and complex aortic plaque on imaging (defined as features of mobility, ulceration, pedunculation, or thickness ≥4 mm).	1
A Age 65–74 years	1 point is given for age between 65 and 74 years.	1

LVEF - left ventricular ejection fraction; HFpEF - Heart Failure with preserved Ejection Fraction; HFmrEF-Heart Failure with mildly reduced Ejection Fraction; HFrEF- Heart Failure with reduced Ejection Fraction; BP – blood pressure; CAD - Coronary Artery Disease; PVD - Peripheral Vascular Disease.

with a zero (0) score of CHA_2DS_2-VA. But, antiplatelet therapy is no more recommended, as an alternative to anticoagulation in patients with AF to prevent ischaemic stroke and thromboembolism (4).

When initiating antithrombotic therapy, modifiable bleeding risk factors should be managed to improve safety. This includes strict control of hypertension, advice to reduce excess alcohol intake, avoidance of unnecessary antiplatelet or anti-inflammatory agents, and attention to OAC therapy (adherence, control of time in therapeutic range if on VKAs, and review of interacting medications). When starting antithrombotic treatment, it's crucial to manage modifiable bleeding risks—such as high blood pressure, excessive alcohol intake, and unnecessary use of antiplatelet or anti-inflammatory drugs. Proper adherence to oral anticoagulant (OAC) therapy review of interacting medications are also important for safety.

DOACs improve stroke prevention in AF and should be started early in the ED for eligible patients, considering bleeding risks and continued for at least four weeks after cardioversion.

Physicians must continuously assess the balance between stroke and bleeding risks, as both can change over time and vary by patient. Bleeding risks rarely justify stopping anticoagulation in eligible patients, since the risk of stroke without treatment usually outweighs bleeding concerns. Patients with non-modifiable risk factors (age, renal impairment, previous bleeding, maliganancy, genetic factor, previous stroke, dementia or intracerebral pathology) should be monitored more closely, ideally within a multidisciplinary care framework. (4) Yet many ED clinicians hesitate due to bleeding risks and limited follow-up after the discharge. (71) Weant et al. highlight the gap between guidelines and real-world practice, as many AF patients are discharged without stroke prevention therapy from the ED. (9) Additionally, some trials designed in low-risk patients recommend considering to use OAC's in those with a CHA_2DS_2-VA score of 1, following a patient-centred and shared care approach (72,73).

There are many gaps for managing AF in the ED, one of which is planning for anticoagulation. Also, it is a challenge for emergency physicians to start anticoagulation in patients with atrial fibrillation (AF) of unknown onset or duration longer than 24 hours. In such cases, selecting an appropriate anticoagulant or performing a transoesophageal echocardiogram to rule out left atrial thrombus may be necessary. However, in unstable patients, this approach

carries the risk of delaying urgent procedures. In unstable AF patients with a duration longer than 24 hours, it may be necessary to determine the anticoagulation strategy based on the patient's clinical condition and risk factors. Although the ESC provides a robust scoring system that offers significant decision support for clinicians, in patients with varying clinical scenarios, the recommendations are not as clearly defined for emergency physicians (15).

Disposition management

For patients who are successfully rate-controlled or cardioverted and stable for discharge, a rate control agent (e.g., metoprolol, diltiazem) should be prescribed (9). If already taking a rate control agent, providers should consider increasing the patient's home dose to prevent recurrence of AF.

In addition, in new-onset AF cases, if the CHA_2DS_2-VA score is elevated, patients should be prescribed an direct acting oral anticoagulant (e.g., apixaban, rivaroxaban) (4). Prior to discharge, appropriate counseling on medication adverse effects is critical, especially bleeding risk (9).

Based on AF-CARE model, this counseling should also focus on patient comorbidities and risk factor management, it involves, hypertension and diabetic control, appropriate heart failure therapy, weight loose, management of obstructive sleep apnea, reducing of alcohol use and a tailored exercise. Emergency physicians should counsel their patient and organize an outpatient appointment for monitoring the patients process. Also, emerging evidence underscores the safety and efficacy of DOAC initiation in the ED for eligible patients, with studies showing reduced stroke risk without significantly increasing bleeding complications when DOACs are started early in high-risk patients (15,74).

Conclusion

Atrial fibrillation is a significant health issue in our modern age, primarily stemming from longer life expectancy, obesity, and sedentary lifestyles. As a result, emergency departments are expected to care for a growing number of new atrial fibrillation patients in the near future. Emergency physicians play a crucial role in detecting and providing early treatment for this condition, as well as initiating the necessary steps for long-term monitoring in other healthcare facilities. Therefore, emergency physicians and emergency departments should be integrated into the atrial fibrillation care (AF-CARE) framework, which includes staff education and appropriate healthcare organization.

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ORIGINAL ARTICLE / IZVORNI ZNANSTVENI ČLANAK

IS THE QUANTITATIVE MEASUREMENT OF IMMATURE GRANULOCYTES ON SYSMEX XN-1000 HEMATOLOGY ANALYZER TRULY RELIABLE?

JE LI KVANTITATIVNO MJERENJE NEZRELIH GRANULOCITA NA HEMATOLOŠKOM ANALIZATORU SYSMEX XN-1000 DOISTA POUZDANO?

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Abstract

Introduction: The diagnostic and prognostic significance of immature neutrophils has been extensively documented. To ensure rapid response to our clinicians we aimed to verify the reliability of the quantitative measurement of immature granulocytes (IG) on a Sysmex XN-1000 hematology analyzer (HA).

Methods: The verification protocol included the precision study performed on both patient and commercial quality control (QC) samples (repeatability and total precision) and the comparison with the reference manual method (light microscopy) according to CLSI H20-A2:2007 guidelines. Two blood smears were prepared and stained using the May Grünwald Giemsa (MGG) technique. Two experienced medical laboratory scientists differentiated all duplicate stained slides.

The method imprecision was expressed as a coefficient of variation in percentages (CV %) and compared to the manufacturer's performance criteria (25.0 % or 0.12 x 10^9/L IG for repeatability; 30 % for total precision). An average bias between the automated method and the manual method was calculated using the Bland-Altman plot and compared to the manufacturer's acceptance criteria (±1.5 % IG). According to the manufacturer, a correlation coefficient between methods should be >0.80. Additionally, a rank correlation between methods was performed. Statistical analysis was performed in MedCalc® v23.1.1 statistical software (MedCalc Software Ltd, Ostend, Belgium)

Results: The repeatability on both patient and QC samples was within the acceptance criteria, ranging from 8.7 % for high IG concentrations to 18.3 % for low IG concentrations. Total imprecision for all concentration levels was within the acceptance criteria (<6 %). One hundred patients were included in the comparison study. IG values ranged from 0.7 to a maximum of 23.3 x 10^9/L. Bland-Altman plot revealed a satisfactory positive absolute bias of 1.2 % IG (95 % CI: 0.9 – 1.5, P<0.0001). Rank correlation revealed a satisfactory correlation coefficient of 0.90 (95 % CI: 0.86 – 0.93, p<0.0001).

Conclusions: The hematology analyzer Sysmex XN-1000 meets all the manufacturer's specifications regarding quantitative IG measurements. The method has been verified and is suitable for daily routine work within the six-part differential blood count, thus significantly improving turnaround time in severe cases where every second to diagnosis count.

Keywords: complete blood count; immature granulocytes; smear review; Sysmex; hematology analyzer (HA)

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Sažetak

Uvod: Dijagnostički i prognostički značaj nezrelih neutrofila detaljno je dokumentiran. Kako bismo osigurali brzu reakciju prema našim kliničarima, cilj nam je bio provjeriti pouzdanost kvantitativnog mjerenja nezrelih granulocita (IG) na hematološkom analizatoru Sysmex XN-1000.

Metode: Protokol verifikacije uključivao je ispitivanje preciznosti na uzorcima bolesnika i komercijalnim kontrolnim uzorcima (ponovljivost i ukupna preciznost), te usporedbu s referentnom ručnom metodom (svjetlosna mikroskopija) prema smjernicama CLSI H20-A2:2007. Pripremljena su i obojena dva razmaza krvi tehnikom May Grünwald Giemsa (MGG). Dva iskusna medicinsko-laboratorijska inženjera razlikovala su sve duplikate obojenih razmaza. Nepreciznost metode izražena je kao koeficijent varijacije u postocima (CV %) i uspoređena s kriterijima proizvođača (25,0 % ili 0,12 x 10^9/L IG za ponovljivost; 30 % za ukupnu preciznost). Prosječna pristranost između automatizirane i ručne metode izračunata je pomoću Bland-Altmanovog dijagrama i uspoređena s prihvatljivim granicama proizvođača (±1,5 % IG). Prema proizvođaču, korelacijski koeficijent između metoda trebao bi biti >0,80. Također je provedena rang-korelacija između metoda. Statistička analiza provedena je u softveru MedCalc® v23.1.1 (MedCalc Software Ltd, Oostende, Belgija).

Rezultati: Ponovljivost na bolesnicima i QC uzorcima bila je unutar prihvatljivih granica, u rasponu od 8,7 % za visoke koncentracije IG do 18,3 % za niske koncentracije IG. Ukupna nepreciznost za sve razine koncentracije bila je unutar prihvatljivih granica (<6 %). U studiju usporedbe uključeno je 100 pacijenata. Vrijednosti IG kretale su se od 0,7 do 23,3 x 10^9/L. Bland-Altman dijagram pokazao je zadovoljavajuću pozitivnu apsolutnu pristranost od 1,2 % IG (95 % CI: 0,9 – 1,5, P<0,0001). Rang-korelacija pokazala je zadovoljavajući koeficijent korelacije od 0,90 (95 % CI: 0,86 – 0,93, p<0,0001).

Zaključak: Hematološki analizator Sysmex XN-1000 ispunjava sve specifikacije proizvođača u vezi kvantitativnog mjerenja IG. Metoda je verificirana i prikladna za svakodnevni rutinski rad u sklopu šestodijelne diferencijalne krvne slike, čime se značajno poboljšava vrijeme obrade u hitnim slučajevima, gdje je svaka sekunda do dijagnoze važna.

Ključne riječi: kompletna krvan slika; nezreli granulociti; pregled razmaza; Symex; hematološki analizator

Introduction

Immature granulocytes are early-stage neutrophilic cells that mature in the bone marrow before being released into the bloodstream. The production of mature granulocytes is affected by outer or inner stimuli of the bone marrow. An increased number of immature granulocytes (IGs) in the peripheral blood is an indicator of emergency granulopoiesis, a response mechanism of the bone marrow leading to releasing premature granulocytes to the bloodstream. A high IG count can be found in cases of infection, inflammation, and sepsis, but also diseases of bone marrow [1]. Although the white blood cell count continues to attract the most attention, it is least useful, and evidence suggest that emphasis should be shifted to other complete blood count (CBC) parameters, one of which is the IG fraction [2,3]. Immature granulocyte percentage is a useful marker to predict infection and its severity [4].

Elevated immature granulocyte count is associated with severe outcomes and can indicate infection, inflammation, or sepsis.

Clinical decision

The IG count can act as an indicator for sepsis and inflammatory conditions such as rheumatoid arthritis [5, 6, 7]. According to a study by Georgakopoulou et al., greater IG values were associated with severe and critical cases of SARS-CoV-2 infection [8]. Other infections, such as febrile urinary tract infections in children can use the IG count as an early detection marker [9]. In neonates, it is considered that immature granulocytes can be present in peripheral blood in smaller amounts, as a response to bone marrow's high production of cells. Ianni et al. have even tried to

establish a reference interval for such values for newborn population [10]. In some other immature to total neutrophil ratio (I/T ratio) of newborn population has been explored as an indicator of early onset neonatal sepsis [11]. Nigro et al. have also studied the newborn population, and their results and conclusions were similar, but referred only to the IG count [12]. Meanwhile, Wettin et al. have found that low counts of immature granulocytes may indicate neonatal infection [13]. One study of pregnant women has shown immature granulocytes to be an independent risk factor for predicting gestational diabetes mellitus, preterm delivery and macrosomia [14]. The diagnostic use of immature granulocytes is highly explored for different infections and inflammatory conditions, and the results are pointing out that the IG count is largely underutilized. It can also be combined with other inflammatory markers, such as CRP, to assess the severity of an inflammatory condition as it can be determined from routine laboratory test results and requires no additional intervention or cost [15,16].

Automated hematology analyzers (HA) such as the Sysmex XN-1000 are widely used to perform the complete blood count and offer information on abnormal cells such as immature granulocytes, abnormal lymphocytes and blasts. The IG count comprises metamyelocytes, myelocytes and promyelocytes. Blasts and band neutrophils are not considered immature granulocytes.

Manual microscopy is still the reference method for IG %, according to CLSI H20-A2 guidelines [17]. It's time and labor intensive and demands significant expertise. Also, a manual count is often imprecise, as it is composed of a relatively small number of cells. Additionally, it's susceptible to human error and subjective judgement. In contrast, the IG count given by the automated HA is available in only a few minutes, which is particularly important for laboratories with high throughput. Also, the results are consistent, standardized and more uniform.

Sysmex XN-1000 is a widely used hematology analyzer and immature granulocytes show great results as an indicator of inflammatory and infectious conditions. Patient samples used in our study comprised all samples with a measured value of IGs, resulting in a wide range of values 0.7 – 23.3 % IG. Taking in all the samples with an IG value ensured a variety of conditions causing immature cells appearing in the bloodstream. The differences in study results on the IG % threshold and protocols used to evaluate the IG concentration measurement encouraged us to analyze XN-1000 by the CLSI and ICHS guidelines [17,18,19]. All the inconsistencies regarding the IG % threshold and trustworthiness of the Sysmex HAs pose a problem with reporting assessment of the IG % parameter within the six-part differential. The aim of this study was to verify the quantitative IG count of the Sysmex XN-1000 HA and to assess its degree of association with the manual count with the goal of reducing blood film review rate without compromising clinical reliability.

Materials and Methods

The experimental study was performed during October and November 2024 at the Department of Medical Laboratory Diagnostics, University Hospital Sveti Duh, Zagreb, Croatia. The verification protocol included analyzing Precision, Comparability, Limit of Blank (LoB) and Accuracy (comparability with the reference method) [20].

Precision, Comparability and Limit of Blank

A short precision study was conducted including repeatability and total precision. The repeatability study was performed using three patient samples in three different concentration ranges and commercial quality control samples SYSMEX XN CHECK™ (lot 4246, exp: 11/24) on three concentration levels, across 20 replicates. The total precision study was carried out utilizing commercial quality control samples SYSMEX XN CHECK™ (lot 4246, exp: 11/24) on three levels, repeated over a 30-day period.

Since the study on immature granulocytes was performed on two identical Sysmex XN-1000 analyzers, a short comparison study was performed to ensure data comparability was maintained. Forty patient samples were included in the comparison study.

Verification of the Limit of Blank (LoB) was achieved by measuring a blank sample (containing only water) across 20 replicates [21].

Manufacturers' acceptance criteria for the Precision, Comparability and Limit of Blank were used. Coefficients of variation (CVs) were compared.

Accuracy

The accuracy of the Sysmex XN-1000 HA on IG concentration measurement was established by comparison to the reference method, a manual smear review. One hundred whole blood K_2EDTA samples were collected, broadly varying in the IG concentration range. The accuracy was verified through comparing the IG count by the Sysmex HA to the IG count obtained by the smear review. Blood smears were stained using the May Grünwald Giemsa (MGG) staining technique and examined on the Olympus BX53 microscope. For every blood sample, two smears were prepared, and a 200-cell manual differential was performed by two experienced medical laboratory professionals, according to CLSI H20-A2:2007 guidelines [17]. The number of promyelocytes, myelocytes and metamyelocytes counted by the manual smear review were added together, in order to enable comparison to the IG% count offered by the Sysmex HA.

Statistical analysis

The precision study results were expressed as imprecision for both repeatability and total precision and were reported as coefficient of variation [CV (%)]. An average bias was calculated using the Bland-Altman plot for both

Table 1. Results of the repeatability study for measurement of immature granulocytes on Sysmex XN-1000 hematology analyzer

REPEATABILITY	PATIENT SAMPLES						QC SAMPLES						SYSMEX XN-1000 CRITERIA	
	L	CV ABS	M	CV %	H	CV %	XN 1	CV ABS	XN 2	CV %	XN 3	CV %	Concentration	Bias %
IG (x10^9/L)	0.1	0.04	0.11	10.8	0.12	19.6	0.078	0.03	0.22	9.2	0.52	8.1	IG>0.10 x 10^9/L	25.0 % or ± 0.12 IG
IG %	1.02	0.35	2	18.3	6.39	10.2	2.6	0.89	3.2	9.9	3.1	8.7	WBC>4.0, IG %>2.0 %	25.0 % or ± 1.5 % IG

L, M, H- patient samples with low, medium and high concentration of immature granulocytes.
XN 1, 2, 3- quality control samples for Sysmex XN-1000 (Level 1, Level 2 and Level 3).
Green color- acceptable results.

the comparison between the Sysmex HA, as well as the comparison between the automated and manual method. The latter was employed in assessing the accuracy of the Sysmex's IG count. In addition, a rank correlation for both comparisons was performed. Statistical analysis was performed in MedCalc® v23.1.1 statistical software (MedCalc Software Ltd, Ostend, Belgium). All the results were evaluated in contrast to the manufacturer's acceptance criteria. $p<0.05$ was considered statistically significant.

Results

Precision

The repeatability results presented in Table 1 were within the acceptance criteria (25.0 % or 0.12 x 10^9/L IG) on all three concentration levels for both patient and quality control samples. The QC samples showed slightly lower CV (up to 9.9 %) rather than patient samples (which were up to 19.6 % for high IG concentrations). The total precision results from the quality control samples were also within the manufacturer-defined acceptance criteria (30 %) and are demonstrated in Table 2.

Comparability and LoB

Strong correlation (correlation coefficient 0.98, 95 % CI: 0.97 – 0.99, $p<0.0001$) that exceeds the established manufacturers criteria (correlation coefficient>0.40) was observed between the analyzers. The verification of the Limit of Blank also matched the criteria, with all results.

Accuracy

The accuracy results were calculated using IG count obtained by the manual smear review as the reference method. The Bland-Altman plot revealed a positive average bias of 1.2% IG (95% CI: 0.9 – 1.5, $p<0.0001$), which aligns with the manufacturer's criteria (±1.5% IG). Rank correlation showed a satisfactory correlation coefficient of 0.90 (95% CI: 0.86 – 0.93, $p<0.0001$), which also corresponds to the defined criteria (correlation coefficient>0.80).

Discussion

The Sysmex XN-1000 HA meets the defined manufacturer's IG count specifications. It shows great results within the precision study (comprising repeatability and total precision), comparability study between analyzers and LoB verification. To assess its accuracy, we compared the XN-1000's IG counts with those obtained by manual microscopy, the established reference method, according to CLSI H20-A2:2007 guidelines. Our results indicate that Sysmex HA delivers reliable and reproducible IG counts within the six-part differential, suggesting that its

Table 2. Results of the total precision study for measurement of immature granulocytes on Sysmex XN-1000 hematology analyzer.

TOTAL PRECISION	QC SAMPLES			SYSMEX XN-1000 CRITERIA		
	XN CHECK 1	XN CHECK 2	XN CHECK 3	XN CHECK 1	XN CHECK 2	XN CHECK 3
IG (x10^9/L)	4.4	3.1	6	30	30	25
IG%	3.8	2.8	3.2	30	30	25

XN CHECK 1, 2, 3- quality control samples for Sysmex XN-1000 (Level 1, Level 2 and Level 3).
Green color- acceptable results.

automated IG measurements are sufficiently accurate for clinical use.

An overestimation bias was observed on the automated IG count compared to manual microscopy, consistent with findings from previous studies also done on Sysmex's hematology analyzers [22,23,24]. By evaluating a significantly larger cell population, the automated system detects lower IG levels that manual counts might miss due to their smaller sample size. Nevertheless, the positive bias remains within the manufacturer's specifications.

Serrando Querol et al. compared the Beckmann Coulter DxH 900 to Sysmex XN20 analyzer and found that the DxH 900 shows better agreement for the IG count in all cases with manual microscopy, and also confirmed previously mentioned positive bias, especially for samples with IG % > 5 % [24]. Linko-Parvinen et al. have suggested utilizing different thresholds on Sysmex XN-1000 whether the IG % is reported or not. If the IG % is reported within the six-part differential, they suggest the threshold for a smear review to be 6 %, and if it is not reported they find the 3 % threshold more adequate [25]. When comparing the Sysmex XN-2000 to Horiba Yumizen H2500, the statistically significant difference of the IG % was explained by differences in methods used by the HAs. The Yumizen H2500 uses the impedance method in addition to the flow cytometry method to count immature granulocytes, in contrast to the XN-2000 using the fluorescent flow cytometry in all channels [26]. In another study, evaluation of Sysmex XN-9000 for detecting IGs in cases of myeloid neoplasms revealed some inconsistencies between XN-9000 and the manual count and ascribed it to inaccurate IG gating in the scattergram and morphologically abnormalities of immature cells [27]. Starks et al. analyzed autovalidation middleware data and raised the IG % threshold from 2 % to 5%, after finding it prevented 6 % of all samples from being autovalidated on Sysmex XN-9000 [28].

The different results obtained by the mentioned studies can be due to many factors. The specific patient group, e.g. patients with a myeloid neoplasm or children can make the results biased. Variations in protocols, including the use of only one slide in the study, or a smaller total cell count number in the smear review (standard 100-cell differential) deviate from established guidelines, and make the results less reliable. Furthermore, Sysmex HAs use the same method for counting immature granulocytes, but vary from other hematology analyzers, making the threshold harder to standardize. Laboratories that use autovalidation also struggle to assess the accuracy of the flag, as they cannot afford to overlook any cases by autovalidation protocol. The manual smear is prone to different mistakes, such as losses due to the fact that IGs are larger cells located at the feathered ends of the smear and smaller total cell count, besides the already mentioned reasons.

The reliability of the automated IG count supports its potential to alleviate a heavy workflow by reducing the smear review rate. The analyzer's reproducibility and consistency minimize the subjectivity and excess labor associated with a manual smear review. Furthermore, the HA generates the IG count within minutes as part of the six-part differential, improving turnaround time and workflow efficiency.

Emergency medicine relies on rapid turnaround, and the Sysmex XN-1000 provides automated, reliable IG counts within every CBC, enabling results within minutes for timely clinical decisions.

However, the XN-1000 does not morphologically differentiate between different WBC precursor cells (promyelocytes, myelocytes and metamyelocytes), which could pose a problem with specific patient groups and complex hematology cases. The analyzer's limitations should be considered when setting the IG % threshold for warranting a smear review.

This study evaluates XN-1000's ability to measure immature granulocytes ranging from very low concentrations not reported by the flagging system to very high ones appearing in cases of severe bone marrow response. The analyzers used in our laboratory are comparable and reliably provide IG concentration results.

In summary, the XN-1000 offers trustworthy results and is an efficient alternative to a manual smear review regarding the IG count. To ensure accurate diagnoses, one must take into consideration the automated IG count in context of each clinical case. Sysmex XN-1000 provides reliable quantitative IG measurement results, effectively complementing manual microscopy. Automated IG reporting could be incorporated as a part of the CBC, thus significantly improving turnaround time in severe cases where every second to diagnosis count.

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ORIGINAL ARTICLE / IZVORNI ZNANSTVENI ČLANAK

PREDICTIVE FACTORS OF SUCCESSFUL RETURN OF SPONTANEOUS CIRCULATION (ROSC) IN OUT-OF-HOSPITAL CARDIAC ARREST – A NATIONAL STUDY

PREDIKTIVNI ČIMBENICI USPJEŠNOG POVRATKA SPONTANE CIRKULACIJE KOD IZVANBOLNIČKOG SRČANOG ZASTOJA – NACIONALNA STUDIJA

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Abstract

Introduction: Out-of-hospital cardiac arrest (OHCA) represents a global public health issue with high mortality rates. Resuscitation outcomes depend on various factors that may differ across populations and regions.

Objective: To analyze the predictive factors of a successful return of spontaneous circulation (ROSC) in OHCA, considering the initiation of bystander cardiopulmonary resuscitation (CPR) before the arrival of emergency medical services (EMS), initial cardiac arrest rhythm, and regional differences.

Methods: This prospective study included adult patients who experienced OHCA in the Republic of Croatia during 2024. Data were collected using the standardized Utstein template and included variables such as age, cause, location of the event, telephone-guided instructions, bystander CPR, initial rhythm, and signs of life at hospital handover. Data analysis was conducted using IBM SPSS Statistics 25.0. Categorical variables were analyzed using the χ^2 test, and binary logistic regression was applied to identify predictors of successful ROSC ($p < 0.05$).

Results: Bystander CPR before the arrival of emergency services resulted in successful ROSC in 33.2 % of cases. Regarding the initial rhythm, ventricular fibrillation was associated with the highest ROSC success rate of 34.6 %. Regional differences were also observed, with variations in success rates between urban and rural areas, including the City of Zagreb.

Conclusion: The importance of early bystander intervention and rapid defibrillation in improving OHCA outcomes has been confirmed. Ventricular fibrillation as the initial rhythm and regional disparities in emergency medical service access and infrastructure further influence the chances of successful ROSC, highlighting the need for targeted education and improved resource availability.

Key words: cardiopulmonary resuscitation; out-of-hospital cardiac arrest; predictive factors; spontaneous circulation

Sažetak

Uvod: Izvanbolnički srčani zastoj (engl. *Out-of-hospital Cardiac Arrest, OHCA*) predstavlja globalni javnozdravstveni problem s visokom stopom smrtnosti. Ishod reanimacije ovisi o različitim čimbenicima koji se mogu razlikovati među populacijama i regijama. Cilj je analizirati prediktivne čimbenike uspješnog

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povratka spontane cirkulacije (engl. *Return of Spontaneous Circulation, ROSC*) kod izvanbolničkog srčanog zastoja, uzimajući u obzir započinjanje oživljavanja od strane očevidaca prije dolaska hitne medicinske službe (HMS), početni ritam srčanog zastoja i regionalne razlike.

Metode i bolesnici: U ovo prospektivno istraživanje uključeni su punoljetni bolesnici koji su tijekom 2024. godine doživjeli OHCA na području Republike Hrvatske. Podaci su prikupljani standardiziranim Utstein obrascem i uključivali su varijable poput dobi, uzroka, mjesta događaja, telefonskih uputa, reanimacije od strane očevidaca, početnog ritma i znakova života pri predaji u bolnicu. Analiza podataka provedena je pomoću IBM SPSS Statistics 25,0. Kategorizirane varijable analizirane su pomoću χ^2 testa, a za identifikaciju prediktora uspješnog ROSC primijenjena je binarna logistička regresija ($p < 0,05$).

Rezultati: Kardiopulmonalna reanimacija započeta od strane očevidaca prije dolaska hitne medicinske službe rezultirala je uspješnim ROSC-om u 33,2 % slučajeva. Početni ritam ventrikulske fibrilacije povezan je s najvećom stopom uspješnosti ROSC-a od 34,6 %. Uočene su i regionalne razlike, s varijacijama u stopama uspješnosti između urbanih i ruralnih područja, uključujući Grad Zagreb.

Zaključak: Potvrđena je važnost rane intervencije očevidaca i brze defibrilacije u poboljšanju ishoda OHCA. Ventrikulska fibrilacija kao početni ritam te regionalne razlike u dostupnosti i infrastrukturi HMS-a dodatno utječu na izglede za uspješan ROSC, naglašavajući potrebu za ciljanim obrazovanjem i unapređenjem resursa.

Ključne riječi: kardiopulmonalna reanimacija; izvanbolnički srčani zastoj; prediktivni čimbenici; spontana cirkulacija

Introduction

Out-of-Hospital Cardiac Arrest (OHCA) represents one of the primary challenges in global healthcare and is a significant cause of mortality worldwide. Despite substantial advancements in cardiopulmonary resuscitation (CPR) techniques and the widespread implementation of early defibrillation strategies, the survival rate of patients experiencing OHCA remains unsatisfactory (1). The global incidence of this condition is high, posing a serious health threat that necessitates continuous efforts to improve access to emergency medical services and public education.

Survival following OHCA varies significantly depending on geographic location, emergency medical service infrastructure, and the level of bystander education. Even in highly developed countries with well-equipped healthcare systems and extensive emergency service coverage, survival rates often remain below 10 % (2). These statistics not only highlight variability in clinical outcomes but also underscore the complexity of factors influencing resuscitation success. Key determinants include the availability and response time of emergency services, as well as the ability and willingness of bystanders to promptly and effectively perform CPR.

The outcomes of OHCA are also closely linked to sociodemographic and clinical characteristics of patients, including age, sex, pre-existing medical conditions, and specific circumstances such as the location and timing of cardiac arrest. Elderly patients or those with pre-existing cardiovascular diseases often have poorer prognoses (3). Additionally, socioeconomic factors, such as access to medical care and individual educational status, can significantly influence the likelihood and outcome of an intervention.

Out-of-hospital cardiac arrest has low survival rates worldwide, with early bystander action, fast emergency response, and initial rhythm crucial; return of spontaneous circulation predicts outcomes.

Return of Spontaneous Circulation (ROSC) is a key objective of emergency medical intervention following OHCA and is considered an essential indicator of resuscitation quality. Achieving ROSC is not only a critical step in stabilizing the patient but also a significant predictor of long-term survival and post-arrest quality of life (1). In the context of acute medical care, rapid and effective resuscitation leading to ROSC can substantially reduce in-hospital mortality and improve recovery outcomes.

Several key factors influence resuscitation outcomes and the likelihood of successful ROSC, including the initial cardiac arrest rhythm, patient age and sex, and the presence of bystanders capable of providing early resuscitation measures (4). Initial cardiac arrest rhythms such as ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) are associated with a higher likelihood

of successful ROSC due to their greater responsiveness to defibrillation. Conversely, asystole and pulseless electrical activity (PEA) often indicate poorer prognoses and require more complex and prolonged interventions to achieve ROSC (5).

The presence of bystanders plays a crucial role in OHCA outcomes, as they can initiate CPR and potentially use an Automated External Defibrillator (AED), significantly increasing survival chances (6). The application of an AED by bystanders before emergency services arrive is particularly critical in cases of VF and VT, where each minute without defibrillation decreases survival probability by 7 % to 10 % (7).

In Croatia, the organization of emergency medical services is structured at the county level through Emergency Medicine Institutes. The emergency medicine network regulates the number, composition, and types of teams operating in different regions to ensure nationwide coverage. This system ensures that at least one emergency team is available within a 25-kilometer radius. Overall, there are 709 Type 1 (T1) teams, 205 Type 2 (T2) teams, and 31 standby teams across 21 county emergency institutes. A T1 team consists of a medical doctor, a nurse, and a driver, while a T2 team includes a specialized nurse or technician and a driver. Emergency services are organized through ambulance transport, with helicopter services available for secondary interventions on islands (8).

Emergency medical services in Croatia are organized by county, ensuring full coverage with T1 and T2 teams available within 25 km, including helicopter support for islands.

The aim of this study was to analyze predictive factors for successful return of spontaneous circulation in out-of-hospital cardiac arrests, considering the initiation of bystander CPR before the arrival of emergency medical teams, the initial cardiac arrest rhythm, and regional differences.

Methods and patients

This prospective study included adult patients who experienced sudden cardiac arrest in out-of-hospital settings. Data were collected from January 1, 2024, to December 31, 2024. The study encompassed all adult patients who suffered sudden cardiac arrest in out-of-hospital conditions within the territory of the Republic of Croatia.

For data collection, the standardized Utstein template was used, which is a mandatory part of medical documentation in out-of-hospital emergency medical services (according to Article 19, Annex 7 of the Regulation on Conditions, Organization, and Mode of Emergency Medicine Operations, Official Gazette 71/2016). The form was completed by emergency medical service personnel who had been previously trained in proper documentation procedures. Additionally, Emergency Medicine Institutes received written instructions to standardize data collection according to the recommendations of the International Liaison Committee on Resuscitation (ILCOR).

Table 1. Distribution of Participants by County

	COUNTY	N	%
EMERGENCY INSTITUTE	Bjelovar-Bilogora	156	2.0
	Brod-Posavina	251	3.3
	Dubrovnik-Neretva	239	3.1
	City of Zagreb	367	4.8
	Istria	575	7.5
	Karlovac	242	3.2
	Koprivnica-Križevci	235	3.1
	Krapina-Zagorje	319	4.2
	Lika-Senj	177	2.3
	Međimurje	163	2.1
	Osijek-Baranja	484	6.3
	Požega-Slavonia	102	1.3
	Primorje-Gorski Kotar	846	11.1
	Sisak-Moslavina	372	4.9
	Split-Dalmatia	1133	14.8
	Šibenik-Knin	275	3.6
	Varaždin	229	3.0
	Virovitica-Podravina	152	2.0
	Vukovar-Srijem	320	4.2
	Zadar	435	5.7
	Zagreb County	567	7.4
	Total	**7640**	**100.0**

The collected data included general patient characteristics such as age, cause, and location of the event. Event and outcome-related data encompassed the provision of telephone CPR instructions, bystander CPR, initial cardiac arrest rhythm, and the presence of signs of life upon hospital admission.

Statistical Methods

Data were analyzed using the IBM SPSS Statistics software (version 25.0). Continuous variables (age) were assessed for normal distribution using the Kolmogorov-Smirnov test. The data were presented as means and standard deviations. Categorical variables were reported as absolute and relative frequencies. Differences between groups were analyzed using the χ^2 test for categorical variables.

Binary logistic regression was employed to model predictive variables associated with successful ROSC before hospital arrival. Statistical significance was set at $p < 0.05$.

Results

Participants based on regional distribution

The local distribution of participants included in the study (N = 7.640) is presented in Table 1. The highest number of participants was recorded in Split-Dalmatia County, with 1.133 (14.8 %), while the lowest number was observed in Požega-Slavonia County, with 102 (1.3 %).

Sociodemographic and clinical characteristics of participants

The study included 7.640 participants, with asystole being the predominant cardiac arrest rhythm (46.5 %). Medical causes accounted for the majority of cardiac arrests (72.0 %). Signs of life during CPR were recorded in 10 % of participants, while at the time of hospitalization, this percentage dropped to 7.5 %, indicating a low survival rate to hospital admission. Most participants were male (64.9 %) with an average age of 70.77 years, which aligns with epidemiological data suggesting a higher prevalence of cardiovascular diseases among older men (Table 2).

Table 2. Sociodemographic and Clinical Characteristics of Participants

Participant Characteristics		N	%
Cardiac Arrest Rhythm	Asystole	3552	46.5
	Unknown	678	8.8
	PEA	745	9.8
	VF	512	6.7
	VT	36	0.5
Cause of Cardiac Arrest	Asphyxia	256	3.4
	Medical	5503	72.0
	Other	1382	18.1
	Overdose	43	0.6
	Electric shock	4	0.1
	Traumatic	351	4.6
	Drowning	101	1.3
Signs of life during cardiopulmonary resuscitation	Yes	766	10.0
	No	4946	64.7
	Not recorded	1927	25.2
Signs of Life at Hospital Admission	Yes	570	7.5
	No	5136	67.2
	Not recorded	1933	25.3
Sex	Male	4961	64.9
	Female	2675	35.0
Age	(mean; SD)	70.77	26.39

Resuscitation depending on initiation of bystander CPR before Emergency Mecial Services (EMS) team arrival

Data on both the outcome and the initiation of bystander CPR were recorded for 4.315 participants. The results indicate a statistically significant association between initiated bystander resuscitation and the ROSC outcome ($p < 0,001$) (Table 3). Among participants who received bystander CPR, 33.2 % achieved successful ROSC, while 19.5 % did not. In contrast, among those who did not receive bystander CPR, 44.4 % achieved ROSC, whereas 55.9 % had a negaative outcome. Although the success rate of ROSC appears higher in the non-bystander CPR group, the significantly higher proportion of unsuccessful resuscitations in this group suggests that bystander CPR may play a critical role in reducing the total number of unsuccessful resuscitations. These findings highlight the importance of public education on basic life support (BLS) techniques to improve survival rates before emergency medical services (EMS) arrive.

Table 3. Outcome of Resuscitation Based on Initiated Bystander CPR

		ROSC *				
		Successful		Unsuccessful		p**
		N	%	N	%	
Bystander CPR	Yes	189	33.2	1004	19.5	<0.001
	No	253	44.4	2869	55.9	

* ROSC - return of spontaneous circulatin
CPR - cardiopulmonary resuscitation
** value derived from the $\chi 2$ test

Outcome of the resuscitation procedure depending on initial rhythm

Data on the outcome of the resuscitation procedure based on the initial rhythm was available for 5706 participants. The results show a statistically significant association between the initial rhythm of cardiac arrest and the outcome of ROSC ($p<0.001$). The highest ROSC success rate was seen with ventricular fibrillation (VF) at 34.6 %. Patients with asystole, the most common initial rhythm, had a successful ROSC in only 18.6 % of cases, while 53.1 % of cases resulted in an unsuccessful resuscitation. Pulseless Electrical Activity (PEA) recorded 21.1 % successful and 9.9 % unsuccessful ROSC (Table 4). The results confirm that the initial rhythm significantly influences the outcome of resuscitation, with VF having the best prognosis, while asystole and VT indicate lower chances for the return of spontaneous circulation.

Table 4. Outcome of the Resuscitation Procedure Depending on Initial Rhythm

	ROSC *				
	Succesful		Unsuccessful		p**
	N	%	N	%	
Asystole	106	18.6	2727	53.1	
PEA	120	21.1	509	9.9	<0.001
VF	197	34.6	247	4.8	
VT	15	2.6	16	0.3	

* ROSC - Return of Spontaneous Circulation
** value derived from the χ^2 test

Regional differences in ROSC outcomes

The results show a statistically significant difference in the outcome of ROSC among counties (p<0.001) (Table 5), with the City of Zagreb recording the highest proportion of successful ROSCs (14.9 %), while the Split-Dalmatia County had the highest proportion of unsuccessful cases (15.1 %). Counties with higher percentages of successful ROSC include Istria (10.0 %) and Zagreb (6.0 %), while lower percentages of successful cases were recorded in counties such as Virovitica-Podravina (2.3 %) and Međimurje (1.9 %).

Table 5. Differences in ROSC Outcomes by County

	ROSC *				
	Successful		Unsuccessful		
	N	%	N	%	p**
Bjelovar-Bilogora	7	1.2	97	1.9	
Brod-Posavina	17	3.0	160	3.1	
Dubrovnik-Neretva	11	1.9	167	3.3	
City of Zagreb	85	14.9	177	3.4	
Istria	57	10.0	437	8.5	
Karlovac	18	3.2	180	3.5	
Koprivnica-Križevci	16	2.8	203	4.0	
Krapina-Zagorje	27	4.7	178	3.5	
Lika-Senj	12	2.1	153	3.0	
Međimurje	11	1.9	138	2.7	
Osijek-Baranja	35	6.1	326	6.3	<0.001
Požega-Slavonia	21	3.7	68	1.3	
Primorje-Gorski Kotar	39	6.8	438	8.5	
Sisak-Moslavina	24	4.2	310	6.0	
Split-Dalmatia	46	8.1	777	15.1	
Šibenik-Knin	16	2.8	169	3.3	
Varaždin	38	6.7	166	3.2	
Virovitica-Podravina	13	2.3	106	2.1	
Vukovar-Srijem	16	2.8	126	2.5	
Zadar	27	4.7	296	5.8	
Zagreb County	34	6.0	464	9.0	

* ROSC - Return of Spontaneous Circulation
** χ^2

Logistic regression analysis for predicting ROSC

Table 6 presents the results of logistic regression for predicting the likelihood of achieving return of spontaneous circulation (ROSC) by the time of hospital arrival. Among the predictors, age is negatively associated with the outcome, with the probability of ROSC decreasing as age increases [odds ratio (OR) = 0.989, p = 0.003]. Providing layperson CPR has a negative, but weak effect (OR = 0.768, p = 0.034), while providing professional CPR has a highly positive and significant effect (OR = 57 268, p < 0.001). The model explains 26,9 % of the variability in the outcome, highlighting the significance of the included predictors for predicting the outcome.

Table 6. Logistic Regression Results for ROSC

Predictor	Odds Ratio [95% Confidence Interval (CI)]	p
Age	0.989 (0.982 - 0.996)	0.003
Bystander CPR	0.768 (0.602 - 0.980)	0.034
Telephone instructions	0.745 (0.525 - 1.056)	0.098
EMS CPR	57 268 (30 266 - 108 361)	< 0.001

CPR- cardiopulmonary resuscitation
EMS CPR- emergency medical services cardiopulmonary resuscitation

Discussion

The results of this study provide a detailed insight into the factors that significantly affect the success of return of spontaneous circulation after out-of-hospital cardiac arrest in the Republic of Croatia. The analysis shown in Table 3 highlights the significant role of layperson CPR before the arrival of professional medical services, with a ROSC success rate of 33.2 % compared to 19.5 % in cases where layperson CPR was not successfully performed. This data confirms the critical importance of early CPR intervention by bystanders, consistent with the findings of Bednarz et al., who concluded that timely CPR intervention generally improves outcomes for patients after OHCA (9). These findings align with the study by Tabata et al. in Japan, which found that layperson CPR training was associated with higher ROSC rates in patients with out-of-hospital cardiac arrest, pointing to the potential benefits of CPR training for non-healthcare professionals (10). Furthermore, research by Siman-Tov et al. in Israel also supports the notion that victims of out-of-hospital cardiac arrest who receive CPR with dispatcher assistance have higher ROSC rates and more frequent defibrillatory rhythms, indicating the universal value of early intervention in improving OHCA outcomes (11).

International studies also emphasize the importance of public education on CPR techniques and the use of automated external defibrillators. A study conducted by Leeb in New York (12) demonstrated that training civilians can significantly increase intervention success, similar to trends observed in our study. These data suggest that educational programs and policies promoting widespread CPR application are crucial for improving outcomes in OHCA patients, regardless of geographical location.

A more detailed analysis of the impact of the initial rhythm of cardiac arrest on ROSC outcomes, presented in Table 4., reveals that ventricular fibrillation has the highest ROSC success rate at 34.6 %. These results are consistent with the research by Kajino et al. (13), who highlighted that VF, due to its high sensitivity to defibrillation, offers better prognosis compared to other rhythms such as asystole or PEA, which require more complex and prolonged resuscitation procedures. Comparing our results to other relevant studies, such as the one by Wolbinski et al. (14), who also emphasized the advantage of VF over asystole and PEA in the context of out-of-hospital cardiac arrest, further supports global consistency in clinical outcomes related to initial rhythms. Additionally, the study by Meneya et al. (15) for the American Heart Association confirms similar trends, showing that patients with VF have a higher survival rate on hospital arrival compared to those with asystole, further supporting the need for prompt and efficient defibrillation as a key element in resuscitation efforts. According to a study by Bergman et al. (16), VF was identified as the most important predictive factor for successful ROSC and long-term survival following cardiac arrest, which matches our results and highlights the importance of continuous monitoring and education in AED use in public spaces.

Regional variations in ROSC outcomes, documented in Table 5, show significant differences within the country, with particularly high success rates recorded in the City of Zagreb (14.9 %). This result may reflect differences in the availability of resources, expertise, and emergency medical service equipment, suggesting the need to strengthen the healthcare system, especially in counties with lower success rates. Potential solutions include improving education for emergency medical personnel, increasing the availability and quality of medical equipment, and enhancing public awareness and education on CPR and AED use.

Regional variations in ROSC outcomes in Croatia show higher success in urban areas like Zagreb, highlighting the need for better resources and training in less equipped regions.

These regional variations are not unique to Croatia. Similar results have been observed in studies from other countries. For example, a study from the United States showed that urban areas have better outcomes in OHCA cases compared to rural areas, attributed to better access and quicker emergency service interventions (17). In Scandinavia, research conducted in Sweden highlighted that integrated emergency services in larger cities like Stockholm achieve higher successful ROSC rates due to efficient protocols and widespread use of AEDs (18). A study from South Korea highlighted that ongoing public education efforts regarding CPR significantly increase the chances of a successful ROSC, particularly in areas where there previously was low awareness of the importance of early intervention (19). Logistic regression, shown in Table 6, identifies older age as a factor negatively correlated with ROSC outcomes, implying that each additional year of age reduces the chances of successful ROSC (OR = 0.989; p = 0.003). This aligns with widely accepted scientific knowledge confirming that older patients, due to the presence of comorbidities and reduced physiological capacity, often have poorer outcomes after OHCA (20). This correlation between older age and reduced chances for ROSC has also been documented in several international studies. For instance, research conducted in Poland by Lewandowski et al. also demonstrated that as age increases, the likelihood of return of spontaneous circulation decreases, with a particularly significant drop among individuals over 75 years of age (21). Similarly, some studies highlight that there may be resistance to providing maximally aggressive treatment to all patients due to concerns about creating a larger number of survivors with poor functional outcomes (3, 22). These attitudes underline the need to develop specific strategies for managing cardiac arrest in older patients, including rapid diagnosis and tailored resuscitation that takess their special needs and limitations into account.

These international findings suggest that healthcare systems should consider adjusting their resuscitation protocols to improve outcomes for the older population, particularly by strengthening the capacity and education of healthcare providers for interventions tailored to age-specific risk factors and comorbidities. In an international context, the effectiveness of layperson CPR in Croatia is comparable to that observed in other European countries, where it is also recognized as a key factor in improving OHCA outcomes (23). For example, the document "Education, Implementation, and Teams: 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations" suggests that implementing widely accessible layperson CPR education can significantly improve ROSC rates, confirming the importance of early intervention (24). Similar guidelines have been proposed by Ravindra et al., who note that strategies such as social media campaigns can improve awareness, knowledge, and skills related to CPR (25). However, the regional differences present within the country point to the necessity of adapting and implementing locally oriented interventions

that consider the specific conditions, resources, and needs of individual regions. In this context, research from North America (26) has shown that regional protocols and specialized education can significantly improve responses to OHCA, especially in rural areas where response times are longer. These results point to the need for regionally tailored programs that could include mobile teams and trained volunteers to support standard emergency services. In analyzing the Swedish model, Strömsöe et al. conducted a study to describe the application of a CPR education program in Sweden over 25 years and link the data to changes in the percentage of OHCA patients who received CPR from bystanders. In Sweden, CPR education is conducted on a cascade principle: instructor-trainers train educators, who then train rescuers.

Widespread layperson CPR education via regional programs like Sweden's cascade training and North America's local protocols can improve OHCA outcomes, especially in underserved areas, by increasing early intervention and reducing ROSC disparities.

Since 1989, 5.000 instructor-trainers have trained more than 50.000 educators, who have in turn trained nearly 2 million of Sweden's 9 million inhabitants in adult CPR. As a result, the number of layperson CPR attempts in OHCA in Sweden increased from 31 % in 1992 to 55 % in 2007, which could be applicable in the context of Croatia given the similar model of education. Such models, based on broad social cooperation and support, could be key to addressing regional disparities in OHCA outcomes.

Limitations of the study

Despite the use of a national data registry, there are limitations related to the potential variability in documentation and reporting of cases from different parts of the country, which may result in incomplete data on some OHCA cases. Furthermore, the availability of variables within the registry does not encompass all clinically relevant factors that could affect outcomes, potentially limiting the comprehensiveness of the analysis. Also, the study primarily relies on short-term outcomes after resuscitation, without considering long-term survival results and the quality of life of patients, which are key elements for a comprehensive evaluation of CPR intervention effectiveness.

Conclusion

The results of this study clearly demonstrate that early layperson intervention, the initial rhythm of cardiac arrest, and regional disparities are key factors influencing the outcome of return of spontaneous circulation following out-of-hospital cardiac arrests in Croatia. Timely initiation of layperson CPR before the arrival of emergency services significantly increases the chances of a successful ROSC, underscoring the critical importance of expanding CPR training among civilians. Furthermore, ventricular fibrillation as the initial rhythm notably improves the chances of successful resuscitation, highlighting the need for prompt defibrillation. Additionally, regional variations in infrastructure and access to emergency medical care reflect the variability in resuscitation outcomes, suggesting the need for the enhancement and adaptation of healthcare resources and strategies.

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REVIEW ARTICLE / PREGLEDNI ČLANAK

THE AIR MERCY SERVICE OF THE SOUTH AFRICAN RED CROSS THE FLYING DOCTORS AND NURSES OF SOUTHERN AFRICA

ZRAČNA HUMANITARNA SLUŽBA JUŽNOAFRIČKOG CRVENOG KRIŽA – "LETEĆI" LIJEČNICI I MEDICINSKE SESTRE JUŽNE AFRIKE

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Abstract

Starting with a single flight from Oudtshoorn to Cape Town in 1966, the South African Air Mercy Service (AMS) evolved into a comprehensive aeromedical organisation serving South Africa. Today AMS has a fleet of fixed-wing and rotor-wing (helicopter) aircrafts with several bases around the country covering over 300,000 km^2 of land area. AMS has emerged as a vital response to provide essential medical care in remote and underserved areas of South Africa and to enable swift assistance to emergency rescue missions on both land and sea. This article outlines the main features of the AMS' history, operations, and highlights how it helps address the country's healthcare challenges afflicted with limited access to medical facilities, socioeconomic disparities, and a high burden of communicable and non-communicable diseases.

Keywords: air ambulance; flying doctors; air mercy service; red cross; south africa; rescue; healthcare

Sažetak

Počevši s jednim letom iz Oudtshoorna u Cape Town 1966. godine, južnoafrička Zračna humanitarna služba (engl. *Air Mercy Service, AMS)* razvila se u sveobuhvatnu zrakoplovno-medicinsku organizaciju koja djeluje širom Južnoafričke Republike. Danas AMS raspolaže flotom zrakoplova s fiksnim i rotirajućim krilima (helikopterima), s nekoliko baza diljem zemlje koje pokrivaju više od 300.000 km^2 kopnenog područja. AMS je postao ključna služba za pružanje osnovne medicinske skrbi u udaljenim i nedovoljno opskrbljenim područjima Južnoafričke Republike, kao i za brzo reagiranje u hitnim spasilačkim misijama na kopnu i moru. Ovaj članak prikazuje glavne značajke povijesti i djelovanja AMS-a te naglašava kako ova služba doprinosi rješavanju zdravstvenih izazova u zemlji pogođenoj ograničenim pristupom zdravstvenim ustanovama, socioekonomskim nejednakostima i visokim opterećenjem zaraznim i nezaraznim bolestima.

Ključne riječi: zračni hitni prijevoz; "leteći" doktori; zračna humanitarna služba; Crveni križ; Južna Afrika; spašavanje; zdravstvena skrb

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Introduction

How it all began

The history of air ambulances dates back to the early 20th century, when airplanes and helicopters were first utilised during World War I, and the French and British military experimented with aircraft to transport wounded soldiers. After World War II, air ambulances were increasingly adopted for civilians - particularly in remote and rural communities (1).

It was in 1966, that the first air ambulance flew in South Africa, when a civilian patient was transported with a small single engine Cessna 205 aircraft from Oudtshoorn to Cape Town, a distance of 420 km by road (2).

As South Africa is a vast country, it was evident that aviation could potentially provide essential medical help in remote areas, particularly after disasters. In response to this need, the Air Mercy Service (AMS) of the South African Red Cross was initiated and developed as an aeromedical organisation within the South African Red Cross Society (SARCS). This collaboration has enabled AMS to update and expand their fleet and medical services. Since then, AMS has become a beacon of hope, as a non-profit organisation providing medical care and transportation from poorly accessible areas across the entire country - as well as providing outreach and rescue services. The seven fundamental principles of the International Red Cross and Red Crescent Movement are to exhibit humanity, impartiality, neutrality, independence, voluntary service, unity and universality and these principles have been instrumental in shaping the ethos and operations of the work of AMS (2,3)

Due to its rapid growth, the AMS was formed into an independent trust fund in 1994 and has since worked closely with the Departments of Health of the provinces of South Africa (4).

Since it began, AMS has helped people in hard-to-reach places by bringing them medical care and transport.

Healthcare Challenges in South Africa

South Africa faces a multitude of healthcare challenges. The most notable of these are the limited access to medical facilities and specialised medicine, as well as inadequate infrastructure, socioeconomic disparities, and the burden of communicable and non-communicable diseases.

In fact, South Africa has the world's largest population of HIV-positive people - of about 7.1 million - and one of the highest incidences in the world of multi-drug resistant tuberculosis. Furthermore, there is a high burden of trauma that can be correlated with severe violence, road traffic injuries and substance abuse (5,6).

These challenges are exacerbated by the vast geographic landscape of the country. Even though health services are provided largely free of charge, the monetary and time costs of travel to a clinic continue to pose a significant barrier to access (7). Additionally, there is a very uneven distribution of tertiary hospitals as higher level care is limited to the major cities.

Figure 1: Pilatus PC12 fixed-wing aircraft of The South African Red Cross Air Mercy Service.

The healthcare system consists of a poorly funded public sector serving an overwhelmingly large portion of the population, with inadequate infrastructure, staffing and medication. Approximately 84 % of the population rely on the public system. The remaining 16 % have access to the private sector with significantly more resources (5).

South Africa's healthcare shows stark inequality: 84 % rely on an underfunded public sector, while 16 % use a well-equipped private sector.

The South African Air Mercy Service

Due to the significant inequality gap within South Africa's healthcare system, there has been an increasing need for medical assistance in remote and underserved areas. As an air-ambulance, AMS complements ground-transportation of critically ill or injured patients from rural areas. The AMS extended their fleet with helicopters in 2000, and could then also participate in primary responses and provide both air-sea and air-mountain rescue. Today AMS operates from the Western Cape (Cape Town and Oudtshoorn), KwaZulu-Natal (Durban), Eastern Cape (Mthatha, East London, Gqeberha) and from supportive infrastructure in the Northern Cape and Free State Provinces. It covers an area of 392,789 km^2 and a population of about 25 million people - which is comparable to the population of Australia (8).

The AMS operates with fixed-wing as well as rotor-wing aircraft. The choice of aircraft varies upon distance, basic airport infrastructure on-site, and the patients' clinic. The medical team consists of at least one paramedic for advanced life support (ALS) and one paramedic for Intermediate life support (ILS), both with wide practical experience.

Figure 2: Mountain Rescue Mission with Leonardo AgustaWestland Helicopter AW119.

Because of healthcare inequality in South Africa, AMS is crucial for reaching rural and remote areas, covering a population and territory similar to Australia's.

The Fleet

The fleet consists of fixed-wing Pilatus PC-12 aircraft and rotor-wing Leonardo AgustaWestland AW119 helicopters. Both are specifically designed and equipped for intensive care transportation.

The Pilatus PC-12 aircraft, manufactured in Switzerland, is a single-engine aircraft with a nine-seater cabin with capacity for three patient stretchers. The PC-12 can reach a top speed of up to 450 km/h and is ideally dispatched for operations at a distance of more than 250 km. The aircraft thus allows efficient long-range medical evacuations and transfers. These aircraft require only a short takeoff and can land on small airstrips of up to 500 - 800 m. They are therefore suitable for operations in areas with very limited infrastructure (9,10).

The Leonardo AgustaWestland AW119 helicopter is a single-engine helicopter with an ideal operating radius of 200 kilometres and a maximum cruise speed of 250 km/h. It has full hoist, sling and winch capabilities, so that rescue missions are possible. As these aircraft can access inaccessible locations, they can assure a rapid response to emergencies on land and on water (9,1).

Flying Doctor Outreach Program

One notable initiative of AMS is the KwaZulu-Natal (KZN) outreach program. This initiative targets rural communities in the KwaZulu-Natal province. Through this program, AMS dispatches medical specialists, including many volunteers, to rural healthcare facilities. In local hospitals, they offer specialised treatments on site and even perform minor surgery and interventions (11). There is also a huge element of skills development and capacity building for all healthcare professionals at these rural facilities. Given that it could take up to two days by road to access tertiary care, this program not only reduces referrals to distant facilities, but also alleviates the lack of specialists and infrastructure in district hospitals (12).

AMS's KwaZulu-Natal outreach program delivers specialized care to rural communities, reducing long hospital trips, and supports local healthcare training.

Facts and Statistics

In 2022, AMS carried out a total of 1131 missions in the Western Cape from the bases in Cape Town and Oudtshoorn – including 687 rotor wing and 444 fixed wing missions. During these missions, they provided medical care to a total of 1207 patients. For the entire year, a distance of 310,699 km was covered by fixed-wing aircraft, and 195,959 km by rotor wing, giving a combined airtime of 1685 hours (9).

The largest share of rotor-wing missions (47 %) was for general medical cases, followed by trauma at 20 % and neonatal care at 22 %. Nearly 30 % of all patients were transported in intubation. Interfacility transfers accounted for 75 % of all rotor-wing missions, whereas 20 % involved rescue missions. Of the rescue missions, 88 were performed on land and 14 at sea (9).

Challenges and Outlooks

The AMS service operates throughout the year. While flights are able to take off on most days, there may be restrictions due to adverse weather conditions, such as high winds, fog, and ice. Rural and remote communities often face infrastructural problems, such as missing air landing strips or unlit runway due to lack of maintenance, vandalism or

Figure 3: Pilatus PC 12 fix-wing aircraft

Figure 4: MD Caroline Egger visiting AMS at Cape Town Base.

the so-called "loadshedding". Loadshedding results in hour-long power cuts in South Africa, which means that existing runway strips are unusable at night. Such restrictions severely limit missions in the dark, especially for fixed-wing aircrafts.

In any of those cases, AMS closely coordinates with ground transportation. Given the very limited number of ambulances serving in remote regions, this results in additional depletion of local resources (12).

In the future, the AMS would like to expand their medical services. One area in which they are attempting to provide additional support is to start a new programme to address the shortage of surfactant for premature infants in rural areas. Emergency transportation of surfactant to the rural doctors is currently under discussion.

Despite weather and infrastructure challenges, AMS coordinates with ground transport to access remote areas and aims to resolve surfactant shortages for premature infants in rural communities.

Conclusion

The South African Air Mercy Service exemplifies the humanitarian ideals of the Red Cross/ Red Crescent Movement, by addressing healthcare challenges and bridging gaps in South Africa's healthcare system. AMS continues to save lives, provide relief during emergencies, and empower communities with valuable healthcare services. As South Africa moves forward, the work of AMS remains crucial in ensuring equitable access to healthcare.

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PRIKAZ SLUČAJA / CASE REPORT

URTIKARIJA - SIMPTOM KOJI SKRIVA IZNENAĐENJE

URTICARIA - WHEN THE OBVIOUS HIDES THE UNEXPECTED

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Sažetak

Urtikarija, ili koprivnjača, je jedan od najčešćih razloga dolaska u hitnu službu i često se smatra kao bezazleno kliničko stanje koje se uspješno liječi antihistaminicima. No, što kada se iza naizgled tipičnog osipa krije nešto daleko ozbiljnije? Predstavljen je slučaj 35-godišnje bolesnice koja se javljala u hitnu službu zbog akutne urtikarije koja nije odgovarala na standardnu terapiju. Daljnja dijagnostička obrada, uz primjenu ultrazvuka, otkrila je aktivnu hidatidnu bolest, uzrokovanu ehinokoknom cistom jetre. Ovaj slučaj naglašava važnost širokog diferencijalno dijagnostičkog pristupa pri procjeni bolesnika s atipičnim ili terapijski rezistentnim oblicima urtikarije, jer u rijetkim slučajevima može upućivati na ozbiljnu osnovnu bolest, zahtijevajući pravovremeno prepoznavanje i ciljano liječenje.

Ključne riječi: cistična ehinokokoza; ehinokokoza; urtikarija; ultrazvučna dijagnostika

Abstract

Urticaria, or hives, is one of the most common presenting symptoms for which patients seek medical attention. It is often considered as a benign clinical condition that responds well to antihistamines. However, what if an apparently typical rash masks a far more serious underlying issue? A case of 35-year-old female patient who repeatedly visited the emergency department due to acute urticaria that did not respond to standard therapy is described. Further diagnostic evaluation, including ultrasound imaging, revealed active hydatid disease caused by a hepatic echinococcal cyst. This case highlights the importance of a broad differential diagnostic approach when assessing patients with atypical or treatment-resistance urticaria, as in rare cases, it may indicate a serious underlying condition, requiring timely recognition and targeted treatment.

Key words: cystic echinococcosis; echinococcosis; urticaria; diagnostic ultrasound

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Uvod

Urtikarija je čest simptom zbog kojeg se traži medicinska pomoć, a procjenjuje se da se tijekom života pojavljuje kod svake pete osobe (1). Klinički se očituje pojavom uzdignutih, crvenkastih kožnih promjena različite veličine i oblika, praćenih izraženim svrbežom. Najčešće nastaje kao posljedica reakcije tip I, posredovane imunoglobulinom E (IgE), pri čemu su glavni uzroci hrana, lijekovi i ubodi insekata. Osim alergijskih reakcija, urtikarija se može pojaviti i u sklopu infekcija uzrokovanih virusima, bakterijama ili parazitima. Ipak, u većine bolesnika uzrok urtikarije ostane nepoznat (2).

Zbog izražene nelagode i svrbeža, bolesnici često zahtijevaju liječenje, iako se osip obično povlači spontano unutar 24 sata (3). U liječenju se primarno koriste antihistaminici, pri čemu se preporučuje primjena antihistaminika druge generacije (npr. loratadin, desloratadin), koji imaju manji sedativni učinak zbog slabijeg prolaska kroz krvno-moždanu barijeru. Međutim, u kliničkoj praksi i dalje prevladava uporaba antihistaminika prve generacije (npr. kloropiraminklorid) (4). Osim toga, učestala primjena sistemskih kortikosteroida u liječenju urtikarije i drugih alergijskih reakcija pokazala se štetnom, budući da je povezana s povećanim rizikom od sepse, zatajenja srca i gastrointestinalnog krvarenja (5). Iako se urtikarija najčešće povezuje s alergijskim reakcijama, u određenim slučajevima može biti simptom ozbiljne osnovne bolesti, što zahtijeva pažljivu procjenu bolesnika i dijagnostičku obradu.

Iako je urtikarija često benigno i samoograničavajuće stanje, u nekim slučajevima može ukazivati na ozbiljnu bolest, što zahtijeva temeljitu kliničku procjenu i dijagnostički pristup.

Prikaz slučaja

Tridesetpetogodišnja bolesnica ponovno se javila u hitnu službu zbog urtikarije koja traje unazad tri dana. Zbog istih tegoba prethodno je pregledana kod svog obiteljskog liječnika, kao i u hitnoj službi. Liječena je parenteralno kloropiraminom (*Synopen*®), metilprednizolonom (*Solu-Medrol*®) i peroralno desloratadinom, ali bez poboljšanja. Tijekom pregleda u hitnoj službi, osim osipa i svrbeža, bolesnica nije imala drugih simptoma koji bi upućivali na težu alergijsku reakciju. Vitalni znakovi bili su uredni, disanje bez smetnji, bolova i drugih tegoba nije bilo. Ponovljena je parenteralna terapija, no simptomi su i dalje bili prisutni, zbog čega je bolesnica zadržana na opservaciji. Laboratorijska obrada pokazala je eozinofiliju, dok su ostali nalazi bili uredni. Ultrazvučni pregled uz krevet bolesnika (engl. *point-of-care ultrasound*, *POCUS*) otkrio je septiranu cističnu tvorbu u jetri s manjom količinom tekućine oko ciste (Slika 1). Na temelju nalaza postavljena je sumnja na ehinokoknu bolest, zbog čega je bolesnica hospitalizirana na odjelu infektologije, gdje je započeto liječenje albendazolom. Planiran je operacijski zahvat. Kompjuterizirana tomograija trbuha (engl. *Multislice Computed Tomography, MSCT*) potvrdila je septiranu cističnu tvorbu veličine oko 5 cm u desnom režnju jetre s uskim pojasom tekućine oko ciste, bez slobodne tekućine u ostatku trbuha. Sljedeći dan cista je operacijski u potpunosti uklonjena. Patohistološka analiza potvrdila je ehinokoknu bolest pronalaskom skoleksa ehinokoka u sadržaju ciste. Nastavljeno je liječenje albendazolom, a bolesnica je kasnije otpuštena kući. Na kontrolama nije bilo znakova povrata bolesti ni ponovne pojave urtikarije.

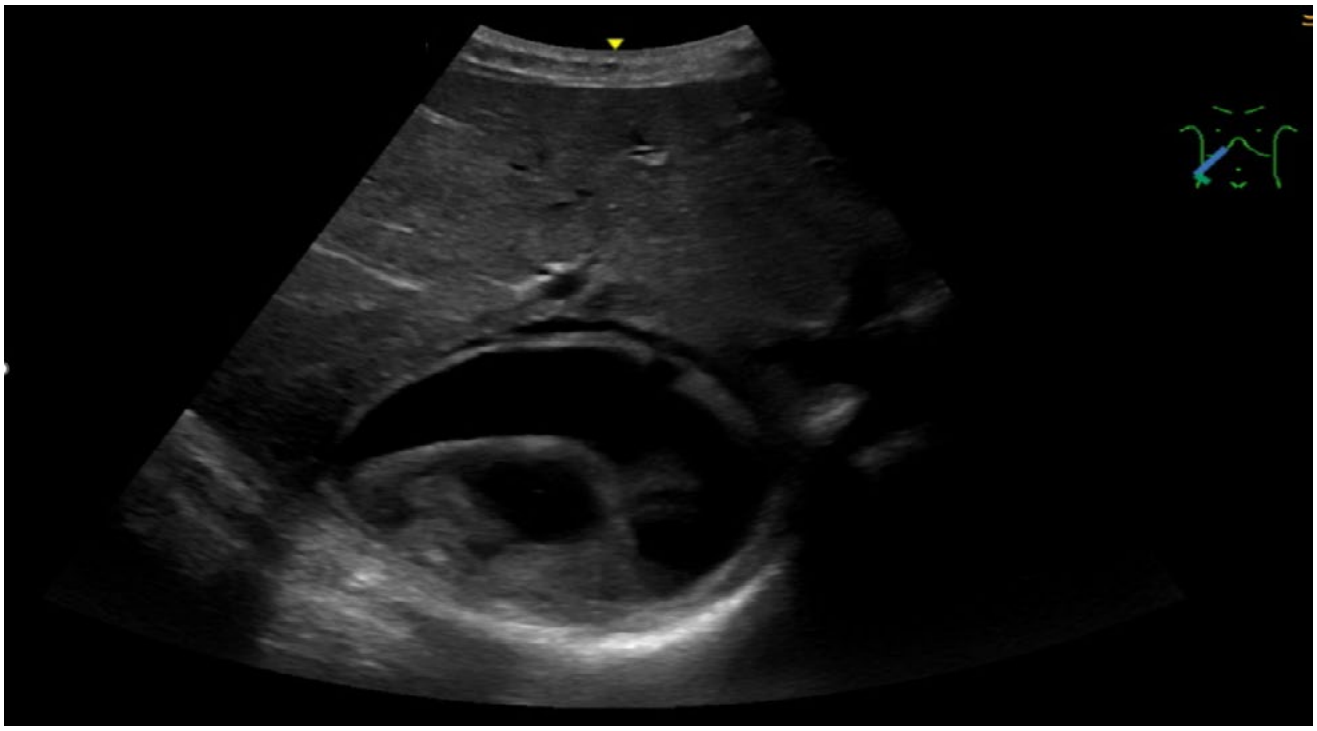
Rasprava

Imunološke reakcije opisane su u oko 25 % slučajeva rupture ehinokokne ciste, najčešće u obliku urtikarije, dok u težim slučajevima može doći do i do razvoja anafilaktoidnog šoka (6). Iako klinička slika može nalikovati IgE-posredovanoj alergijskoj reakciji, u ovom slučaju radi se o nespecifičnoj imunološkoj reakciji uzrokovanom oslobađanjem parazitskih antigena u okolna tkiva i cirkulaciju. Oslobađanje antigena potiče aktivaciju mastocita, degranulaciju i oslobađanje histamina, što rezultira pojavom simptoma nalik klasičnoj alergijskoj reakciji.

Ehinokokoza je zoonoza uzrokovana trakavicama *Echinococcus granulosus* i *Echinococcus multilocularis*. *E. granulosus* uzrokuje cističnu ehinokokozu, dok *E. multilocuraris* uzrokuje alveolarnu ehinokokozu (7). Odrasli oblik *E. granulosus* parazitira u psima, dok se prijelazni oblik razvija u preživačima (8). Bolest se prenosi feko-oralnim putem, najčešće kontaktom s psećom dlakom, ali i putem kontaminiranog tla, neopranog povrća ili kontaktom s preživačima (9). Čovjek je slučajni domaćin, u kojem se parazit ne razvija do odraslog oblika, već ostaje u fazi hidatidne ciste, pri čemu ciste rastu brzinom 1-50 mm godišnje (10).

Ruptura ehinokokne ciste izaziva nespecifičnu imunološku reakciju zbog oslobađanja parazitskih antigena, što može dovesti do urtikarije ili anafilaktoidnog šoka aktivacijom mastocita i upalnih medijatora.

Ehinokokna bolest najčešće zahvaća jetru (50-70 %), a nešto rjeđe pluća (11). Većina bolesnika je asimptomatska sve do razvoja komplikacija, koje se javljaju kod otprilike jedne trećine oboljelih (12). Najčešća komplikacija je ruptura ciste, koja je praćena diseminacijom bolesti i imunoloških reakcija nalik alergijskim, od kojih je najopasniji



Slika 1. Ultrazvučni prikaz septirane cistične tvorbe u jetri

anafilaktoidni šok, dok se sekundarna infekcije ciste rjeđe razvija. Najčešći simptomi rupture hidatidne ciste su bol u trbuhu, mučnina, povraćanje i urtikarija. Bolesnica tijekom cijelog razdoblja, od pojave urtikarije do hospitalizacije, nije imala znakove akutnog intraabdominalnog zbivanja. To se može objasniti činjenicom da je ruptura ciste bila djelomična i lokalizirana, bez diseminacije tekućine u trbušnu šupljinu.

Eozinofilija se uočava u manje od 15 % slučajeva i obično se javlja tek u slučaju rupture ciste. Pojava eozinofilije u bolesnika s urtikarijom trebala bi pobuditi sumnju na postojanje parazitske bolesti (13). U prikazu slučaja, rekurentna urtikarija praćena eozinofilijom potaknula je daljinu ultrazvučnu obradu. Sumnja na rupturu ehinokokne ciste postavljena je tek nakon što je ultrazvučno pronađena septirana cista u jetri. Ultrazvuk je metoda izbora za dijagnozu i praćenje. Kompjuterizirana tomografija i magnetna rezonancija pružaju detaljniji uvid u anatomske odnose ciste i okolnih struktura. Svjetska zdravstvena organizacija (SZO) klasificira ciste kao aktivne, koje sadrže septe, neaktivne, koje sadrže kalcifikacije, te prijelazne oblike (14). Ovisno o stupnju dijagnostičke potvrde, bolest se može smatrati mogućom, vjerojatnom i dokazanom (15). Bolest se smatra mogućnom kod svih bolesnika kod kojih je slikovnim metodama pronađena suspektna cista. Vjerojatnom se smatra ako je uz slikovni prikaz potvrđena i s najmanje dva pozitivna serološka testa, dok se dokazanom smatra kada su patohistološkom analizom u uklonjenoj cisti ili aspiriranom cističnom sadržaju dokazane strukture skoleksa. Pri obradi prikazane bolesnice ultrazvuk je bio presudan za brzu dijagnozu bolesti i započinjanje odgovarajuće terapije te planiranje daljnjeg tijeka liječenja. Prijeoperacijski je učinjen MSCT trbuha kako bi se omogućilo planiranje operacijskog zahvata.

Pojava urtikarije uz eozinofiliju, bez jasnog alergijskog uzroka, treba potaknuti sumnju na parazitsku infekciju poput ehinokokoze.

Liječenje se provodi antiparaziticima iz skupine benzimidazola, najčešće albendazolom, u dozi 10-15 mg/kg dnevno, što u odraslih obično iznosi 800 mg dnevno, podijeljeno u dvije doze uz obrok. Uz antiparazitsku terapiju preporučuje se i kirurško uklanjanje ciste u potpunosti, uz dugotrajno praćenje tijekom narednih deset godina kako bi se pravovremeno prepoznala eventualna rekurencija bolesti (16). Prethodno elektivnom uklanjanju nekompliciranih hidatidnih cista uporaba albendazola u trajanju osam tjedana pokazala se uspješnom u pretvaranju aktivnih cisti sa živućim skoleksima u neaktivne ciste u kojima su nametnici mrtvi (17). Ruptura ehinokokne ciste uzrokuje rasap infektivnog sadržaja po okolnim organima. U slučaju rupture nužno je odmah započeti profilaksu alergijske reakcije i provesti hitan operacijski zahvat (18,19). Cilj operacije je spriječiti širenje bolesti, ukloniti cistu i smanjiti rizik od recidiva. Radikalni pristup uključuje resekciju okolnog tkiva i potpuno uklanjanje

ciste, što povećava rizik od perioperacijskih komplikacija, ali češće dovodi do izlječenja. Konzervativni pristup podrazumijeva otvaranje ciste i uklanjanje sadržaja, lakše se izvodi, no nosi veći rizik od recidiva, kasnijeg mortaliteta i morbiditeta (14).

Zaključak

Urtikarija je čest simptom u hitnoj službi koji u većini slučajeva ima benignu i prolaznu etiologiju. Međutim, kod bolesnika s perzistentnim oblicima potrebna je šira dijagnostička obrada kako bi se isključili ozbiljniji uzroci. U prikazu slučaja, ultrazvučna obrada uz krevet bolesnika postavila je sumnju na hidatidnu bolest, što je omogućilo brzo usmjeravanje daljnje dijagnostike i pravovremeno započinjanje odgovarajućeg liječenja. Ovaj slučaj naglašava važnost cjelovitog pristupa bolesnicima s nespecifičnim simptomima, korištenje šire diferencijalne dijagnoze te vrijednost ultrazvučne dijagnostike u hitnoj medicini i kliničkoj praksi.

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PREGLEDNI ČLANAK / REVIEW ARTICLE

ZBRINJAVANJE BOLESNIKA S KRONIČNOM BUBREŽNOM BOLESTI U SLUČAJU PRIRODNIH KATASTROFA

MANAGEMENT OF PATIENTS WITH CHRONIC KIDNEY DISEASE IN CASE OF NATURAL DISASTERS

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Sažetak

Cilj je ovog rada pružiti spoznaje za zbrinjavanje bolesnika s kroničnom bubrežnom bolesti u slučaju najčešćih prirodnih katastrofa vodeći se najnovijim dokazima i preporukama. MEDLINE i Web of Science baze podataka su pretražene koristeći kombinacije ključnih riječi "kronična bubrežna bolest", "katastrofe" i "zbrinjavanje katastrofa". Relevantni istraživački radovi te trenutne smjernice internacionalnih društava su analizirani kako bi se ekstrapolirale preporuke i prilagodbe prakse optimalne za pravilno postupanje i planiranje u slučaju katastrofičnih situacija.

U ovome radu predočene su mogućnosti intervencija u smislu kontrole nastale štete i jasnih uputa zbrinjavanja u katastrofičnoj situaciji neovisno o kojoj se katastrofi etiološki radi s ciljem osiguranja kvalitete života bolesnika uz optimizaciju zdravstvenog sustava.

Ključne riječi: katastrofe; kronična bubrežna bolest; preraspodjela

Abstract

The aim of this paper is to provide a concise guide to successful management in catastrophic situations in patients with chronic kidney disease while referencing the latest evidence and recommendations. A search of the literature was conducted using the MEDLINE and Web of Science databases, using combinations of keywords "chronic kidney disease", "catastrophic situation" and "management of catastrophes." The relevant original research papers and current international society guidelines were analysed in order to extract relevant recommendations and practice modifications optimal for the reduction of this unexpected situation. Regardless of aetiology and type of catastrophic situation, there are certain interventions proven to reduce the problem and improve both the patients' quality of life and the efficiency of healthcare system resource utilization.

Key words: catastrophic situation; chronic kidney disease; reallocation

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Utjecaj prirodnih katastrofa na svakodnevno funkcioniranje

Prirodne katastrofe su nepredvidljive pojave koje u vrlo kratkom vremenskom razdoblju uzrokuju značajnu materijalnu, logističku i drugu štetu. Bilo da je riječ o potresu, požaru, tsunamiu, uraganu ili globalnoj pandemiji neviđenih razmjera posljednjih nekoliko godina, svaka prirodna katastrofa značajno mijenja uvjete svakodnevnog rada i funkcioniranja te zahtijeva brojne prilagodbe, inovativna logistička rješenja i preraspodjelu postojećih resursa kako bi se ostvarila razina funkcioniranja sustava najbliža onoj prije nastale štete.

Prirodne katastrofe mogu ozbiljno ugroziti svakodnevno funkcioniranje zdravstvenog sustava, osobito u zbrinjavanju bolesnika koji zahtijevaju kontinuiranu skrb, poput onih s kroničnom bubrežnom bolešću.

Kod zbrinjavanja nefrološkog bolesnika ozlijeđenog tijekom prirodnih katastrofa, ključno je pravovremeno prepoznavanje sljedećih stanja:

1. Bolesnik s "crush" sindromom uslijed masivne traume mišića (najčešće uslijed zatrpavanja u potresu) s mogućim razvojem akutnog oštećenja bubrega (AOB).
2. Bolesnik s akutnim sindromom odjeljka (engl. *acute compartment syndrome*).

Za obje skupine bolesnika, od velike je važnosti odgovarajuća hidratacija, koja se provodi parenteralnom infuzijom u količini od 3-6 litara/24 sata, uzimajući u obzir demografske i kliničke specifičnosti bolesnika (star/mlad bolesnik, dosadašnje bolesti/bez bolesti). Ako bolesnik nema venski pristup, infuzija se može primijeniti putem intraosealnog pristupa. U slučaju anurije, volumen infuzije potrebno je smanjiti na 1 litru/24 sata, uz dodatak tekućine kako bi se kompenzirali gubici nastali tijekom razdoblja kada bolesnik nije bio odgovarajuće hidriran. Pravovremeno uključivanje fasciotomije i amputacije ekstremiteta u bolesnika sa sindromom odjeljka u cilju spašavanja života predstavlja ključnu stavku u zbrinjavanju ove skupine bolesnika. Također, nužno je pravovremeno započeti s akutnom nadomjestnom bubrežnom terapijom (ANBT) u bolesnika s akutnim oštećenjem bubrega.

3. Bolesnik s kroničnom bubrežnom bolešću (KBB) koji nije u programu dijalize.

Bolesnik iz ove skupine može doživjeti akutizaciju KBB-a, odnosno pogoršanje postojeće bubrežne bolesti uslijed dehidracije i stanja opisanim u točkama 1 i 2. U ovoj skupini bolesnika potrebno je razmotriti i one kojima su nedostupni lijekovi za liječenje drugih kroničnih nezaraznih bolesti (poput srčane bolesti, dijabetesa, hipertenzije, demencije i dr.), što može obuhvatiti značajan broj bolesnika s KBB-om. Također, treba imati na umu bolesnike s presađenim organima koji uzimaju imunosupresivne lijekove, a koji, uslijed prirodnih nepogoda, mogu ostati bez pristupa potrebnoj terapiji, što može dovesti do ozbiljnih komplikacija.

4. Bolesnik s kroničnom bubrežnom bolesti u programu hemodijalize i peritonejske dijalize.

Bolesnici koji zahtijevaju kontinuiranu skrb i praćenje, poput onih s bubrežnom bolešću završnog stadija na hemodijalizi, predstavljaju osobito ranjivu skupinu tijekom prirodnih katastrofa. Studije koje su retrospektivno analizirale bolničku dokumentaciju tijekom potresa pokazale su da su potresi, bez obzira na lokaciju, uzrokovali propuštanje tretmana hemodijalize, hitne premještaje, zatvaranje centara za dijalizu, oštećenje opreme i smanjenje strateških i logističkih mogućnosti za pružanje nadomjestne bubrežne terapije (1-4). Slično se odnosi i na druge prirodne katastrofe, poput uragana i poplava. Primjerice, nakon uragana Katrina 2006. godine u New Orleansu u Sjedinjenim Američkim Državama (SAD), više od polovice medicinskih ustanova koje su pružale hemodijalizu lokalnom stanovništvu privremeno je obustavilo rad zbog sanacije štete ili nedostatka resursa za neprekinuto funkcioniranje, što je dovelo do propuštanja 1-3 tretmana hemodijalize kod većine lokalnih bolesnika na kroničnom programu hemodijalize (5). Također, COVID-19 kao nedavna biološka katastrofa je doveo do neviđenog preopterećenja zdravstvenih sustava i bolničkih kapaciteta diljem svijeta, postavljajući imperativ reorganizacije postojećih sustava i uvođenja inovativnih rješenja za suočavanje s novonastalim izazovima (6).

Brza reorganizacija i uvođenje inovativnih rješenja postaju nužnost kako bi se osigurao kontinuitet zdravstvene skrbi u ovim ekstremnim uvjetima.

Lekcije naučene iz povijesti i od "susjeda"

Jedna od, ako ne i najveća, prednost globalizacije jest mogućnost razmjene informacija i učenja od sustava koji su nadvladali izazove za koje želimo biti spremni. Neki od tih sustava, primarno sustavi u Japanu i SAD-u, su u posljednjih 25 godina prepoznali najveće zapreke brzom i učinkovitom povratku normalnog funkcioniranja tijekom prirodne katastrofe te su poduzeli mjere implementiranja rješenja za uklanjanje istih.

U nastavku navodimo ona koja smatramo najvažnijima, a koja su posebno vezana za bolesnike s kroničnom bubrežnom bolesti te populaciju na hemodijalizi.

Planiranje

Učinkovito planiranje je temelj otpornosti zdravstvenog sustava na prirodne katastrofe. To uključuje izradu

protokola za krizne situacije, osiguravanje alternativnih lokacija za dijalizu, uspostavljanje lanaca opskrbe lijekovima i potrošnim materijalom, kao i evidentiranje bolesnika ovisnih o nadomjestnoj bubrežnoj terapiji. Ključna komponenta plana je i međuinstitucionalna suradnja te jasna podjela odgovornosti među timovima. Sustavi koji su ranije definirali jasne smjernice i operativne planove za izvanredne situacije pokazali su bržu stabilizaciju i bolju zaštitu bolesnika.

Edukacija bolesnika

Tijekom prirodnih katastrofa, nerijetko se dogodi prekid ili zastoj u komunikaciji putem uobičajenih kanala (TV program, mobilne mreže, online portali), stoga je ključno pripremiti bolesnike koji su u programu hemodijalize na mogućnost prirodne katastrofe koja dovodi do gubitka pristupa lokalnoj ustanovi za dijalizu te im pružiti jasne upute za postupanje, koje su u skladu s unaprijed dogovorenom i planiranom strategijom za slučaj prirodne katastrofe. Pozitivan primjer takve prakse jest u SAD-u, gdje su nakon uragana Katrina 2006. godine izrađeni edukacijski dokumenti za bolesnike, koji daju preporuke u slučaju izvanredne situacije te upute za prehranu, dezinfekciju vode, odspajanje s uređaja za dijalizu u slučaju hitne evakuacije (7).

Međunarodna iskustva pokazuju da protokoli i edukacija bolesnika smanjuju prekide terapije i komplikacije tijekom katastrofa, poboljšavajući kontinuitet skrbi i smanjujući morbiditet.

Priprema dijaliznih ustanova za prirodne katastrofe

Posljedično već spomenutim prirodnim katastrofama, nekoliko je zemalja i međunarodnih društava izdalo smjernice, preporuke i kontrolne liste za dijalizne ustanove, kako bi iste osigurale odgovarajuću razinu pripremljenosti na prirodne katastrofe. Jedna od takvih organizacija je KCER (Kidney Community Emergency Response Coalition), koji je izdao smjernice i upute za hemodijalizne ustanove naziva Pripremljenost za katastrofe: Vodič za ustanove za kroničnu dijalizu (engl. *Disaster Preparedness: A Guide for Chronic Dialysis Facilities*) (8-9). U nastavku prikazujemo neke od najvažnijih smjernica za dijalizne ustanove:

1. Pripremljenost za oštećenje mreže opskrbe električnom energijom/ prekid opskrbe ustanove električnom energijom

Prirodne katastrofe poput potresa često dovode do oštećenja mreže opskrbe električnom energijom. S obzirom na ovisnost moderne opreme i uređaja o električnoj energiji, dijalizne bi ustanove trebale biti pripremljene za situaciju u kojoj je opskrba istom privremeno prekinuta. Takva pripremljenost primarno podrazumijeva postojanje rezervnog generatora električne energije u ustanovama ili pak mogućnost komunikacije, nabave i dopreme istih do ustanove u relativno kratkom vremenskom periodu.

Potrebno je educirati medicinsko osoblje o komponentama hemodijalizatora koje ovise o stalnom dovodu električne energije te o onima koje ostaju funkcionalne kada uređaj prelazi na vlastiti privremeni izvor napajanja (bateriju). Uređaji najčešće omogućuju rad zaslona, krvnih pumpi, alarma za arterijski i venski tlak te senzora za mjehuriće zraka i u režimu baterijskog napajanja, dok su funkcije poput hemodijafiltracije i alarma za transmembranski tlak u takvim uvjetima najčešće onemogućene. Pri prekidu opskrbe električnom energijom, sustav opskrbe vodom se isključuje, a dijaliza se prekida jer nema utoka dijalizata.

U situaciji prekida opskrbe ustanove električnom energijom, poželjno je imati rezervni sustav koji će kompenzirati prestanak funkcije pumpe za krv ukoliko se iscrpe rezervni kapaciteti uređaja (baterija), kako bi se spriječio nastanak ugrušaka. Za tu svrhu postoje ručne pumpe za cirkulaciju krvi, s kojima bi osoblje trebalo biti upoznato te uvježbano za upotrebu istih. Ukoliko je potrebna hitna evakuacija dok je hemodijaliza u tijeku ili su bolesnici spojeni na uređaj za hemodijalizu, potrebno je poznavati tehnike brzog odvajanja bolesnika od uređaja korištenjem stezaljki i škara, pazeći da rezanjem cijevi ne dođe do krvarenja bolesnika. Takve je postupke potrebno usvojiti kroz simulaciju i edukaciju te periodično ponavljati u obliku evakuacijskih vježbi, kako bi osoblje ne samo na hemodijalizi, nego i u hitnim službama bilo odgovarajuće pripremljeno za iste.

Pripremljenost za prekid opskrbe vodom

Osim same dostupnosti vode, u kontekstu hemodijalize važna je činjenica da kvaliteta dopremljene vode također može biti narušena posljedično oštećenju mreže opskrbe vodom. Stoga tijekom i/ili nakon prirodne katastrofe poput potresa treba osigurati ne samo opskrbu vodom, već i integritet sustava za pročišćivanje i obradu vode, kako bi se osigurala voda odgovarajuće kvalitete za hemodijalizu. Ukoliko nije moguće u kraćem vremenskom roku zbrinuti jedan ili oba od navedenih problema, potrebno je imati kontakt s drugom, geolokacijski bliskom ustanovom koja može primiti bolesnike u program hemodijalize dok se problemi vezani uz vodu ne otklone u matičnoj ustanovi.

Priprema "kutije" za izvanredne situacije

Od izrazite je važnosti svaku ustanovu za hemodijalizu opskrbiti kutijama koje sadrže sve što je potrebno za funkcioniranje u izvanrednim situacijama/prirodnim katastrofama. Takve bi kutije trebale sadržavati:

1. Popis kontakt osoba za izvanredne okolnosti/hitnoće svakog bolesnika i djelatnika ustanove

2. Kontaktne informacije lokalne policije, vatrogasaca, tvrtke zadužene za opskrbu vodom, tvrtke zadužene za opskrbu električnom energijom, tvrtke zadužene za održavanje i servisiranje uređaja za pročišćavanje vode
3. Ispisani plan ustanove za slučajeve prirodne katastrofe
4. Ispisane karte s lokacijama rezervnih generatora električne energije, zaliha vode, goriva
5. Traku za zaprječenje ulaza u ustanovu u slučaju evakuacije
6. Setove za prvu pomoć
7. Antimikrobne dezinficijense za osobnu upotrebu i ubruse
8. Maske, jednokratne latex rukavice, jednokratne pregače

Opskrba lijekovima i uloga ljekarnika/farmaceuta u slučaju izvanredne situacije vezano za bolesnike s kroničnom bubrežnom bolesti

Uloga ljekarnika u zajednici može pružiti značajno viši stupanj nefrološke skrbi, posebno vezano uz problem adherencije, poboljšavajući pridržavanje uzimanja propisanih lijekova i utjecati na rane intervencije s pravodobnim podsjetnicima za bolesnikte te mogućnosti adekvatne opskrbe lijekovima (9-10). Svaki bolesnik s KBB-om u pravilu zahtijeva sveobuhvatan i visoko individualiziran pristup. U suradnji s ljekarnikom, a ovisno o stupnju bubrežnog oštećenja (što se procjenjuje za svakog bolesnika), predlažu se individualne prilagodbe u terapiji, što doprinosi boljoj nefrološkoj skrbi, poglavito u kontekstu onemogućenosti pristupa liječniku koji bolesnika inače vodi (10-11).

Najvažnije moguće uloge ljekarnika su:

1. Procjena terapije, budući da bolesnici s KBB-om često koriste brojne lijekove zbog pridruženih bolesti (često i više od 20 tableta dnevno).
2. Omogućiti kućnu dostavu lijekova,
3. Otvaranje"tele-ljekarni" uz pružanje odgovarajućih informacija o lijekovima,
4. Savjetovanje, prepoznavanje i prevencija potencijalnih problema povezanih s lijekovima
5. Promicanje adherencije uzimanja lijekova uz poštivanje etičkih načela, osobito u kontekstu ranjivih bolesnika koji su podložni dodatnim izazovima, kao što su prirodne katastrofe (11).

Ljekarnici unaprjeđuju skrb za bolesnike s kroničnom bubrežnom bolešću optimizacijom terapije, praćenjem adherencije te pravovremenim intervencijama, osobito u kriznim situacijama.

Koordinacija i popis dostupnih resursa

Nakon potresa u Kobeu 1995. godine, japanske su vlasti organizirale sustav zbrinjavanja bolesnika u slučaju izvanredne situacije. Prvi korak u uspostavi takvog sustava je bilo umrežavanje svih ustanova za hemodijalizu te popisivanje njihovih resursa i izmjena informacija o istima na redovnoj bazi (12). Resursi o kojima svaka ustanova šalje informacije uključuju:

1. osobu zaduženu za administraciju u slučaju prirodne katastrofe
2. stanje ustanove u kojoj se odvija hemodijaliza (stanje zgrade, opreme, rezervne opreme)
3. količinu dijalizatora, dijalizata, ekstrakorporealnih sustava
4. broj slobodnih kreveta u jedinici za dijalizu te broj bolesnika koje ustanova može primiti/treba prebaciti u drugu ustanovu
5. broj i vrstu dostupnog osoblja

Ovakav sustav popisivanja dostupnih resursa koji se svakodnevno ažurira je nužan za odgovarajuću organizaciju i pripremu za izvanredne situacije. Isto je provedeno tijekom potresa i COVID-19 pandemije u Republici Hrvatskoj.

Logistika, komunikacija i robne zalihe tijekom/nakon izvanredne situacije

Važno je jasno navesti tko obavlja koju ulogu tijekom izvanredne situacije te tko zbrinjava bolesnike trenutno u programu hemodijalize, kao i sastaviti plan u slučaju ponovne izvanredne sitaucije/prirodne katastrofe ili prolongacije situacije u kojoj su kapaciteti pružanja redovne zakazane skrbi (npr seansi hemodijalize) smanjeni. Za potrebe transporta bolesnika u centre koji su unatoč katastrofi u mogućnosti pružiti im potrebnu skrb, moguće je angažirati lokalne volonterske udruge i koordinirati sve dionike skrbi (bolesnika, liječnike, sestrinsko osoblje, volontere, administraciju bolničkih ustanova).

Po završetku izvanrednog stanja, neophodno je provesti temeljitu analizu postupanja i kvalitete pružene skrbi tijekom same katastrofe/izvanrednog stanja kako bi se prepoznale potencijalne "rupe" u sustavu pružanja skrbi. Sukladno dobivenim podacima i rezultatima, potrebno je razviti strategiju i formulirati jasne upute o daljnjem postupanju u slučaju ponovljene izvanredene situacije (13).

Zaključak

Postupak pripreme za prirodnu katastrofu je iscrpan, kompleksan i multifaktorijalan. Niti najbolje izvedena priprema nije uvijek dovoljna za saniranje štete kakvu može uzrokovati neočekivana prirodna katastrofa.

Ovaj rad ima za cilj osvijestiti i upozoriti na najčešće potencijalne propuste i nedostatke prilikom pripreme sustava zemalja koje su pretrpjele prirodne katastrofe

velike magnitude poput potresa ili drugih nepogoda na koje moramo biti pripremljeni.

Komponente koje su neophodne za odgovarajuću pripremu u slučaju prirodne katastrofe, kako one geološke, tako i biološke obuhvaćaju: edukaciju i pripremu bolesnika; razvoj i implementaciju umreženog, centraliziranog sustava informacija o dostupnim kapacitetima ustanova i robnim zalihama koji se redovito ažurira od strane Ministarstva zdravstva; pripremu samih ustanova za izvanredne situacije (kroz jačanje logistike, infrastrukture, edukaciju osoblja).

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PRIKAZ SLUČAJA / CASE REPORT

SINDROM SUPERHIKA

"SUPERHIK" SYNDROME

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Sažetak

U medicini se ponekad susrećemo sa slučajevima koji zvuče neobično, ali zapravo imaju sasvim logično objašnjenje. Jedan od takvih je i Sindrom Superhika - stanje koje bi legendarni negativac iz serijala *Alan Ford* s ponosnom nosio kao svoje ime. Iako simptomi poput bolova u trbuhu, mučnine i povraćanja možda ne djeluju neobično, njihova povezanost s prekomjernom konzumacijom alkohola i metaboličkim promjenama može dovesti do alkoholne ketoacidoze – potencijalno opasnog stanja koje se lako previdi. I dok bi protivnici u stripu padali u nesvijest od njegovog ubojitog zadaha, u stvarnom životu taj isti simptom može biti znak metaboličkog kaosa koji zahtijeva hitnu intervenciju.

Ključne riječi: alkoholizam; dijabetička ketoacidoza; ketoni; metabolička ketoacidoza

Abstract

In medicine, we sometimes encounter cases that sound unusual but actually have a completely logical explanation. One such case is the "Superhik Syndrome" – a condition that the legendary villain from the *Alan Ford* series would proudly wear as a badge of honor. Although symptoms such as abdominal pain, nausea, and vomiting may not seem unusual, their association with excessive alcohol consumption and metabolic changes can lead to alcoholic ketoacidosis – potentially dangerous condition that can easily be overlooked. And while his opponents in the comics would pass out from his deadly breath, in real life, that very symptom could be a sign of metabolic chaos requiring urgent medical intervention.

Key words: alcoholism; diabetic ketoacidosis; ketones; metabolic ketoacidosis

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Uvod

Alkoholna ketoacidoza (AKA) reverzibilni je oblik metaboličke acidoze koji se najčešće javlja kod pothranjenih osoba nakon prekomjerne konzumacije alkohola, posebno u kontekstu kroničnog alkoholizma (1). Razvoj metaboličke acidoze u AKA rezultat je složenih mehanizama, uključujući opsežan metabolizma alkohola, gladovanje i povraćanje, koji posljedično dovode do nakupljanja ketonskih tijela u organizmu. Konzumacija alkohola često prestaje zbog pojave bolova u trbuhu, mučnine i povraćanja, a bolesnici se javljaju u hitnu službu najčešće jedan do dva dana nakon početka simptoma. U tom trenutku koncentracija alkohola u krvi može biti niska ili nemjerljiva (2,3). Iako se AKA obično očituje normalnom ili sniženom razinom glukoze u krvi, ponekad može biti praćena hiperglikemijom, što može navesti na neispravnu dijagnozu dijabetičke ketoacidoze (DKA) te neodgovarajućeg liječenja inzulinom, povećavajući rizik od ijatrogenih komplikacija (4,5).

Alkoholna ketoacidoza je reverzibilni oblik metaboličke acidoze koji se javlja uslijed prekomjerne konzumacije alkohola, najčešće kod pothranjenih osoba, uz nakupljanje ketonskih tijela.

Naziv „Sindrom Superhika“ inspiriran je legendarnim negativcem iz stripa *Alan Ford* i simbolično prikazuje povezanost AKA, metaboličkih poremećaja i terapijskog postupka ovoga stanja. Superhik, poznat po svojoj nezasitnoj ljubavi prema alkoholu, bio bi pravi medicinski fenomen da su ga liječnici ikada imali priliku pregledati. Nakon konzumacije velikih količina alkohola, stekao bi svoju „supermoć“ – ubojit zadah kojim je omamljivao protivnike, no taj bi učinak oslabio nakon što bi pojeo kolač. Poznato je da unos glukoze kod alkoholne ketoacidoze, kao osnovni terapijski postupak, zaustavlja proizvodnju ketonskih tijela i doprinosi postupnoj uspostavi metaboličke ravnoteže. Iako “Sindrom Superhika” nije medicinski termin, ova analogija uz prikaz slučaja nastoji podići svijest o različitim oblicima ketoacidoze, s posebnim naglaskom na alkoholnu etiologiju, s obzirom na globalni porast konzumacije alkohola i njegovih štetnih posljedica (6).

Prikaz slučaja

Bolesnik u dobi od 35 godina pregledan je u hitnoj službi zbog bolova u trbuhu i povraćanja u posljednja dva dana. Iz anamneze se doznaje za kroničnu upalu gušterače alkoholne etiologije i depresiju, zbog čega je uzimao pankrealipazu, citalopram, zopiklon, tramadol i tiamin. Pri prijemu bolesnik je pri svijesti, tahipnoičan, hemodinamski stabilan, s generaliziranom bolnošću trbuha i pothranjenim statusom (indeks tjelesne mase = 16 kg/m^2). Arterijski acidobazni status pokazao je tešku metaboličku acidozu, hiperketonemiju i hiperglikemiju, dok su ostali nalazi krvi bili uredni (Tablica 1). Na temelju ove biokemijske trijade, započeta je terapija inzulinom i intravenskim tekućinama prema protokolu za DKA. Međutim, unutar sat vremena od početka terapije inzulinom bolesnik razvija hipoglikemiju praćenu slabošću, drhtavicom i preznojavanjem. Primjena inzulina je odmah prekinuta, a uvedena je infuzijska otopina glukoze, što dovodi do povlačenja simptoma i normalizacije glukoze u krvi. Naknadna heteroanamneza otkriva tri prethodne hospitalizacija u zadnjih godinu dana u drugoj bolničkoj ustanovi zbog sličnih simptoma, a svima je prethodila epizoda prekomjernog unosa alkohola. Tijekom prethodnih hospitalizacija, u više je navrata provedena ultrazvučna i CT obrada trbuha, koja je pokazivala masnu jetru. Najviše izmjerena vrijednost glukoze u krvi iznosila je 25 mmol/L, dok je glikozilirani hemoglobin (HbA1c) u svim slučajevima bio unutar referentnih vrijednosti (4,5 - 5,6 %). Ovakav nalaz upućivao je na alkoholnu ketoacidozu kao vjerojatniju dijagnozu. Simptomi su se poboljšali uz analgetike, antiemetike i intravenske tekućine, a razina glukoze ostala je unutar normalnih vrijednosti do otpusta. Bolesniku je pružena psihijatrijska podrška te je kasnije otpušten kući.

Tablica 1. Rezultati laboratorijske pretrage krvi bolesnika

Pokazatelj	Vrijednost	Referentne vrijednosti
pH	7,15	7,35-7,45
pO_2	13,8 kPa	11,1-14,4 kPa
pCO_2	2,90 kPa	4,7-6,4 kPa
HCO_3^-	4,0 mmol/L	21-27 mmol/L
BE	-25,0 mmol/L	-2 do +3 mmol/L
GUK	15,0 mmol/L	4,4-6,4 mmol/L
SpO_2	96 %	96-98 %
Ketoni (S)	6 mmol/L	< 0,5 mmol/L
Ketoni (U)	+	negativno
Laktati	1,4 mmol/L	0,5-2,0 mmol/L
Kalij	3,9 mmol/L	3,9-5,1 mmol/L
Natrij	130 mmol/L	137-146 mmol/L
Urea	3,0 mmol/L	2,8-8,3 mmol/L
Kreatinin	70 µmol/L	64-104 µmol/L
Leukociti	7,4 x109 /L	3,4-9,7 x109 /L
Lipaza	40 U/L	< 67 U/L
Etanol (S)	< 0,1 g/L	0,0 g/L

pH = mjera kiselosti/lužnatosti; pO_2 = parcijalni tlak kisika; pCO_2 = parcijalni tlak ugljikovog dioksida; HCO_3^- = koncentracija bikarbonata u krvi; BE = višak baza (engl. base excess); GUK = glukoza u krvi; SpO_2 = saturacija krvi kisikom; S = serum; U = urin

Tablica 2. Obilježja alkoholne i dijabetičke ketoacidoze - Prilagođeno prema referenci (2).

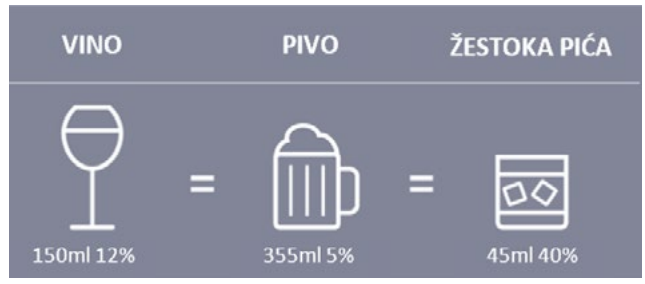
	Alkoholna ketoacidoza	Dijabetička ketoacidoza
Povijest bolesti	kronični alkoholizam, pothranjenost	šećerna bolest (najčešće tip 1)
Precipitirajući čimbenici	epizoda prekomjernog unosa alkohola praćena gladovanjem	infektivno stanje, prekid ili nedovoljna terapija inzulinom
Klinička prezentacija	mučnina, povraćanje, bol u trbuhu	
	simptomi obično na kraju epizode opijanja s postupnim razvojem	poliurija i polidipsija, simptomi s brzim razvojem u roku jednog dana
Fizikalni pregled	dehidracija, hipovolemija, šok	
	bolesnik obično pri svijesti, u kontaktu; zadah po alkoholu i acetonu	bolesnik suženog stanja svijest, konfuzan; zadah po acetonu
Acidobazni status	metabolička acidoza s velikim anionskim manjkom	
Razina glukoze u krvi	obično normalna ili snižena (hiperglikemija u 35 % slučajeva do 15 mmol/L)	teška hiperglikemija (rijetko euglikemija)
Razina etanola u serumu	niska ili nemjerljiva	nije prisutna
Ketoni	hiperketonemija	
	značajno povišen BOHB (10:1)	blago povišen BOHB (3:1)
Elektroliti	hipokalijemija hipofosfatemija hipomagneziemija	hiponatremija hipokalijemija
Liječenje	glukoza, rehidracija tiamin	rehidracija (izotonične otopine), inzulin

BOHB = beta-hidroksibutirat

Rasprava

Zbog sličnih biokemijskih obilježja, razlikovanje AKA od DKA može biti izazovno, stoga je neophodan cjelovit pristup bolesniku, pri čemu se naglasak stavlja na (hetero) anamnezu i povijest bolesti (Tablica 2).

Alkoholna ketoacidoza čini 25 % svih slučajeva ketoacidoze i obično se javlja kod pothranjenih osoba s anamnezom epizode prekomjerne konzumacije alkohola, često u kontekstu kroničnog alkoholizma (7). Epizoda prekomjerne konzumacije alkohola (engl. *binge drinking*), prema Američkom Nacionalnom institutu za zlouporabu alkohola i alkoholizam (engl. *National Institute on Alcohol Abuse and Alcoholism*, *NIAAA*), definira se kao obrazac konzumacije alkohola koji dovodi do koncentracije alkohola u krvi od 0,08 g/L ili više, što bi odgovaralo unosu pet ili više standardnih pića kod muškaraca, odnosno četiri ili više kod žena unutar razdoblja od dva sata (8) (Slika 1).



Slika 1. Količine koje približno odgovaraju jednom standardnom piću (14 g čistog alkohola), prema Američkom Nacionalnom institutu za zlouporabu alkohola i alkoholizam.

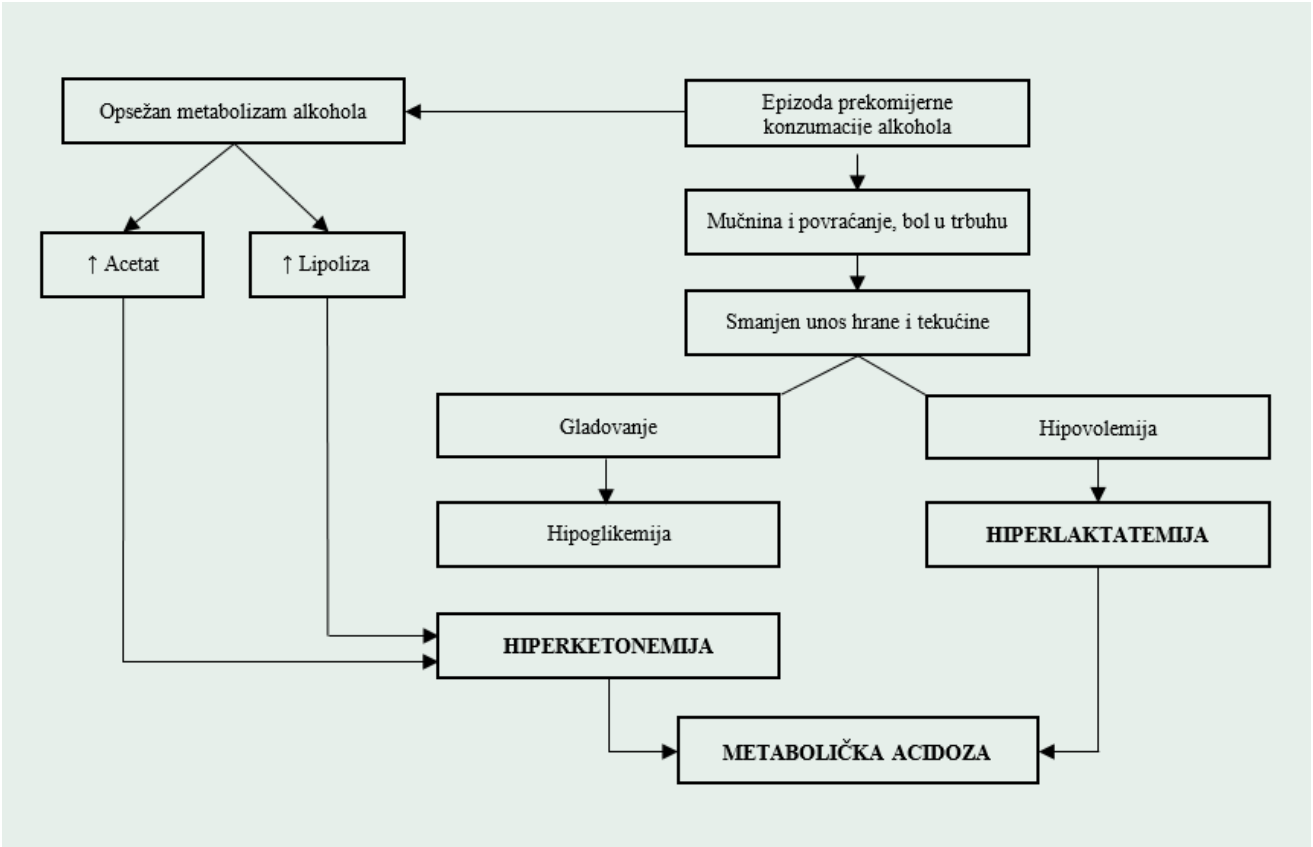
Prilagođeno prema referenci (8).

Iako se ranije smatralo da je AKA češća kod žena, pokazalo se da podjednako zahvaća oba spola (9,2). Nakon epizode prekomjernog konzumiranja alkohola, simptomi poput bolova u trbuhu, mučnine i povraćanja često dovode do prestanka daljnjeg unosa alkohola. Simptomi se razvijaju postupno i mogu biti posljedica akutnog učinka alkohola, uključujući akutnu upalu jednjaka, sluznice želuca i gušterače. Bolesnici se obično u ponavljajućim epizodama javljaju u hitnu službu, najčešće 24 do 48 sati od pojave simptoma, pri čemu razina alkohola u krvi može biti niska ili nemjerljiva (2,3). Kako alkohol u visokim koncentracijama inhibira lipolizu, ketogeneza i razvoj acidoze postaju izraženiji nakon pada njegove razine, što je posljedica povećane aktivnosti katekolamina (posebno noradrenalina) i kortizola. Razina glukoze u krvi najčešće je snižena ili unutar normalnih vrijednosti zbog gladovanja i inhibirane glukoneogeneze u jetri metabolizmom alkohola. Međutim, u 35 % slučajeva AKA se može prezentirati hiperglikemijom koja posljedično nastaje uslijed povećane aktivnosti kontraregulatornih hormona (glukagon, katekolamini, kortizol) i relativnog manjka inzulina, pri čemu je razina glukoze obično blago povišena i rijetko prelazi 15 mmol/L (3,4). Za isključenje kronične hiperglikemije korisno je odrediti HbA1c, koji je kod ovog bolesnika svaki put bio unutar normalnih vrijednosti.

Alkoholna ketoacidoza čini 25 % slučajeva ketoacidoze, a simptomi poput abdominalne boli i mučnine pojavljuju se s vremenskim odmakom, dok prisutna hiperglikemija u trećini slučajeva može zavarati kliničku sliku.

Diferencijalna dijagnoza alkoholne ketoacidoze, osim dijabetičke ketoacidoze, obuhvaća i druga stanja, uključujući akutnu upalu gušterače, upalu žučne sluznice, peptički vrijed, peptički ulkus, hepatitis i Boerhaaveov sindrom (ruptura jednjaka). Također, potrebno je razmotriti i euglikemijsku DKA, koja se češće javlja kod djece, trudnica i bolesnika na SGLT2 inhibitorima. Osim toga, treba uzeti u obzir trovanje metanolom i etilen glikolom.

Metabolička acidoza u AKA rezultat je međusobno povezanih mehanizama, uključujući pojačani metabolizam alkohola, gladovanje, povraćanje i hipovolemiju (Slika 2). Povećana oksidacija alkohola, pod djelovanjem enzima alkohol dehidrogenaze i aldehid dehidrogenaze, dovodi do porasta razine acetata, što posljedično potiče povećanu sintezu ketonskih tijela - acetoacetata i beta-hidroksibutirata (BOHB), pri čemu se dominantno stvara BOHB. Nakon prestanka unosa alkohola nastupa



Slika 2. Patofiziologija alkoholne ketoacidoze
Preuzeto i prilagođeno prema referenci (2).

akutno gladovanje i relativni manjak inzulina, što refleksno aktivira kontraregulatorne hormone (glukagon, katekolamine i kortizol). Njihovo djelovanje dodatno pojačava razgradnju masnih kiselina i ketogenezu. Omjer BOHB i acetoacetata u normalnim uvjetima iznosi 1:1, dok se u DKA povećava na 3:1, a kod AKA taj omjer može doseći čak 10:1 (10). Iako su test trakice za urin standardna metoda za otkrivanje ketonskih tijela, za razliku od acetoacetata, one ne mogu detektirati BOHB jer ne reagira na nitroprusidni test. Međutim, danas su dostupni uređaji nalik glukometrima koji omogućuju brzo i precizno mjerenje BOHB-a iz kapilarne krvi, čime se poboljšava dijagnostika ketoacidoze (11).

Liječenje AKA je jednostavno i učinkovito, a bolesnici brzo postižu kliničko poboljšanje. Osnovni terapijski pristup čini rehidracija i primjena infuzijskih otopina glukoze, čime se prekida ketogeneza i sprječava progresija metaboličke acidoze. Uz to, neizostavna je primjena tiamina, koji pospješuje metabolizam alkohola i sprječava razvoj Wernickeove encefalopatije. Preporuka je primijeniti 500 mg tiamina intravenozno (1). Osim hitnog liječenja, naglasak se stavlja na multidisciplinarni pristup koji uključuje korekciju nutricijskog statusa i edukaciju o važnosti apstinencije od alkohola kako bi se spriječili recidivi i dugoročne posljedice.

Liječenje alkoholne ketoacidoze temelji se na rehidraciji, primjeni glukoze i tiamina, uz multidisciplinarni pristup usmjeren na prevenciju recidiva i komplikacija.

Zaključak

Alkoholna ketoacidoza čest je metabolički poremećaj kod pothranjenih osoba s poviješću kroničnog alkoholizma. Ovaj slučaj ističe važnost prepoznavanja AKA kao moguće diferencijalne dijagnoze kod bolesnika s nespecifičnim simptomima. Poseban naglasak stavlja se na svijest liječnika o različitim oblicima ketoacidoze te važnost dobre (hetero)anamnneze, što doprinosi ranom i točnom postavljanju dijagnoze i primjeni odgovarajuće terapije, smanjujući rizik od ijatrogenih komplikacija.

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REVIEW ARTICLE / PREGLEDNI ČLANAK

FEBRILE SEIZURES IN THE EMERGENCY DEPARTMENT: ASSESSMENT AND MANAGEMENT

FEBRILNE KONVULZIJE U HITNOM BOLNIČKOM PRIJEMU: PROCJENA I ZBRINJAVANJE

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Abstract

Febrile seizures (FS) are the most common neurological disorder in children aged 6 months to 5 years. These seizures are typically benign and occur during a febrile event (at least 38°C), without the presence of central nervous system infections, metabolic disorders, or a history of epilepsy.

The cause of FS seems to be multifactorial. Genetic predisposition has been recognized, although the mode of inheritance is not well known. Fever as a trigger of FS is requisite and up to 82 % of FS occur during viral infections, while bacterial infections are less often as a trigger. Febrile seizures are categorized as: simple or complex. Division is based on the presence of focal signs, duration and recurrence within a single infectious episode.

Prehospital and emergency management should address primarily on stabilizing the child ABC's (airway, breathing and circulation). Most febrile seizures will resolve before children arrive at the Emergency Department. For those that have not resolved and are lasting more than five minutes, benzodiazepine is recommended to terminate the seizure. Rectal diazepam and buccal midazolam are the first choice as rescue therapy, especially if IV access is not available. Prognosis is favorable and there is a low risk of developing epilepsy.

Sažetak

Febrilne konvulzije (FK) su najčešći neurološki poremećaj kod djece u dobi od 6 mjeseci do 5 godina. Najčešće su benigne i javljaju se tijekom febrilnog stanja (najmanje 38°C), bez prisutnosti infekcija središnjeg živčanog sustava, metaboličkih poremećaja ili povijesti epilepsije. Uzroci febrilnih konvulzija su višestruki, a genetska predispozicija je jedan od uzroka, iako način nasljeđivanja nije poznat. Povišena tjelesna temperatura je glavni okidač napadaja, a 82 % febrilnih konvulzija dešava se tijekom virusnih infekcija, dok su bakterijske infekcije rjeđe. Febrilne konvulzije dijele se na jednostavne i složene, a podjela se temelji na postojanju žarišnih ispada, trajanju i ponovnoj pojavi unutar 24 sata.

Većina febrilnih konvulzija prestaje prije dolaska djeteta u hitni bolnički prijem. Djecu čiji napad traje treba stabilizirati (ABC pristup) te zaustaviti napad. Prva linija terapije u zaustavljanju napada su benzodiazepini. Rektalni diazepam i bukalni midazolam su lijekovi izbora ako se ne može uspostaviti intravenski put. Prognoza febrilnih konvulzija je dobra, većina prolazi spontano i ne zahtijeva liječenje te ima nizak rizik od razvoja epilepsije.

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Introduction

Febrile seizures (FS) represent the most common neurological disorder in children aged 6 months to 5 years. FS in childhood are mostly of benign character. They are defined as seizure during a febrile event (at least 38°C) without central nervous system infection, metabolic disorders or history of epilepsy (1).

The prevalence among children ranges between 2% and 5% in Europe and the United States, and up to 12% in some parts of Asia. The peak incidence of first febrile seizure occurs during the second year of children's lives (2). There is a slight male predominance.

Etiology

The cause of FS seems to be multifactorial. Genetic predisposition has been recognized, although the mode of inheritance is not well known. Polygenic inheritance has been suggested (3,4). If a child has febrile seizures there is 10 % to 45 % risk that their siblings will also have one. Susceptibility to FS is linked to several genetic loci such as 2q,5q,8q,19p and 19q. The most robust linkage is on chromosome 2q and specifically to genes responsible for sodium channel receptors and genes responsible for the immune-inflammatory response (5).

The cause of febrile seizures seems to be multifactorial, with genetic predisposition playing a significant role.

Fever as a trigger of FS is requisite and up to 82 % of FS occur during viral infections, while bacterial infections are less often as a trigger (6). The most common viruses associated with FS are: human herpesvirus 6, influenza, parainfluenza, adenovirus, respiratory syncytial virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (7). SARS-CoV-2 causes a febrile illness in children but it is not a trigger for FS. One study reviewed data of 8854 children aged from 0 to 5 years, diagnosed with COVID-19. Only 0.5 % of them were diagnosed febrile seizures (8).

It is still an issue for debate whether the maximum temperature or the rate of temperature rise determines the risk for febrile seizures (3). Temperature above 38°C remains a trigger for onset a febrile seizure.

Clinical signs and symptoms

Febrile seizures are categorized as: simple or complex. Division is based on the presence of focal signs, duration and recurrence within a single infectious episode. 20 % to 35 % of FS are classified as complex and their prevalence increases up to 45 % in children under 12 months of age (9).

Febrile seizures are classified as simple or complex, with complex seizures being more common in younger children and those with previous neurological issues.

A prolonged FS may result in a febrile status epilepticus (FSE). The definition means a continuous seizure (more than 5 minutes) without neurological recovery.

Simple febrile seizures

Simple febrile seizures are generalized tonic-clonic spells, and also tonic-atonic spells can be seen. The facial and respiratory muscles are also involved. They last less than 15 minutes and most of simple FS are shorter, with median duration of 3-4 minutes (10). A deep breath and closed eyes are signs of the end of seizures. Simple FS do not recur in 24-hour period.

After a simple FS children return to baseline condition very quickly and without any neurologic disorders. The postictal period can be associated with confusion or agitation and drowsiness.

Complex febrile seizures

Complex FS can be focal or generalized prolonged seizures, lasting more than 15 minutes. They are recurring in 24 hours during the same illness. Complex FS are associated with postictal neurologic abnormalities: prolonged drowsiness, transient hemiparesis (Todd paresis). Open and deviated eyes are a clinical feature of ongoing seizure.

Children with complex FS are often younger and have more likely abnormal development and previous neurologic impairment.

Diagnostic assessment

Febrile seizure is a clinical diagnosis and is defined by the following features:

1. A child aged between 6 months and 5 years
2. A seizure associated with high fever (≥38°C)
3. Absence of central nervous system infection
4. Absence of acute metabolic disorders that can cause seizures
5. No history of previous febrile seizures and no pre-existing neurologic abnormalities

Main points to examine after the first febrile seizure:

1. Medical history and physical examination to identify fever causes
2. Characteristics and duration of the seizures and post seizure status
3. Family history of FS and epilepsy

4. Pre-existing neurologic abnormalities
5. Recent illness and the use of antibiotics
6. Recent vaccination and immunization status against Haemophilus influenzae type b and Streptococcus pneumoniae

For children with simple FS who are well-appearing, diagnostic testing is unnecessary in most cases. The focus is on the assessment of the underlying febrile illness and parent education about recurrent febrile seizures and low risk of future epilepsy.

Febrile seizures in children 6 months to 5 years are usually benign, but complex cases need careful evaluation and may require lumbar puncture and brain imaging.

Signs for recurrence of FS

1. Age younger than 18 months
2. Fever duration of less than one hour and on lower level of temperature before seizure onset
3. Family history of FS
4. Preexisting neurologic abnormalities

Signs of future risk of epilepsy:

1. Age older than 3 years of the first FS
2. Family history of epilepsy
3. Multiple episodes of FS and complex FS
4. Pre-existing neurologic abnormalities

Children presenting with complex FS, specially if it is the first one, require more individualized approach. Physical and neurologic examination includes attention to:

1. Vital signs
2. Level of consciousness
3. Presence of meningismus
4. Tense or bulging fontanelle
5. Focal differences in muscle tone

Abnormalities in any of these signs should direct us to expanded diagnostics: routine laboratory testing, lumbar puncture, brain multislice computed tomography (MSCT), elective electroencephalography (EEG) and elective magnetic resonance imaging (MRI) of brain.

Indications for lumbar puncture:

1. Signs of meningitis/encephalitis
2. Age under 12 months
3. Unknown/uncomplete immunization status
4. Recent antibiotic treatment (can mask signs of meningitis)

Urgent brain MSCT should be done in children with abnormally large head, abnormal neurologic examination with focal features, or when there are symptoms of increased intracranial pressure (11).

Management

Prehospital and emergency management should address primarily on stabilizing the child ABC's (airway, breathing and circulation). In parallel with the management of convulsions, antipyretic measures should be initiated to reduce body temperature as soon as possible. Most febrile seizures will resolve before children arrive at the Emergency Department (ED).

For those that have not resolved and are lasting more than five minutes, benzodiazepine is recommended to terminate the seizure (12). Rectal diazepam and buccal midazolam are the first choice as rescue therapy, especially if IV access is not available (13). Both of them have rapid onset and limited adverse events (in terms of respiratory depression). Table 1. shows the first-line medication for febrile seizures.

Febrile status epilepticus rarely stops spontaneously and after initial benzodiazepine administration and repeated dose after 5 minutes, there is a need for additional antiseizure medications such as levetiracetam, valproate or phenobarbital (Table 2) (14).

Febrile status epilepticus rarely stops spontaneously and requires prompt intervention with benzodiazepines, followed by additional antiseizure medications if seizures persist."

Table 1. First line medication for febrile seizure

diazepam	0,3-0,5 mg/kg rectally – max dose 20 mg 0,2 mg/kg IV – max dose 10 mg 0,2 mg/kg intranasally – max dose 20 mg
midazolam	0,3-0,5 mg/kg buccally – max dose 10 mg 0,2 mg/kg intranasally -max dose 10 mg 0,1-0,2 mg/kg IM -max dose 10 mg
lorazepam	0,1 mg/kg IV – max dose 4 mg

Table 2. Second line medication for febrile seizure

LEVETIRACETAM	60 mg/kg IV
VALPROATE	20-40 mg/kg IV
PHENOBARBITAL	20 mg/kg IV

Most children with febrile seizures do not require hospital admission and can be safely discharged after a period of observation, provided they return to their neurological

baseline. Before discharge, it is essential to reassure and educate parents on appropriate fever management and symptom monitoring.

Hospital admission should be considered in the presence of any of the following factors: a Glasgow Coma Score (GCS) below 15 more than one hour after the seizure, complex febrile seizures, signs of meningeal irritation, age under 18 months, prior antibiotic use before seizure onset, or incomplete or unknown immunization status.

Conclusion

Febrile seizures are the most common type of seizures in young children with relatively high recurrence rate. Prognosis is favorable and there is a low risk of developing epilepsy. Classification of febrile seizures on simple and complex type is helping ED staff in diagnostic and therapeutic management.

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REVIEW ARTICLE / PREGLEDNI ČLANAK

THE USE OF WHOLE BLOOD TRANSFUSION IN EMERGENCY MEDICINE: A NARRATIVE REVIEW

PRIMJENA TRANSFUZIJE PUNE KRVI U HITNOJ MEDICINI: NARATIVNI PREGLED

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Abstract

Whole blood was the first human blood product to be transfused in modern medicine, seeing widespread use during the final months of World War I. With the advent of blood component therapy and the concept of using intravenous crystalloid fluids for initial resuscitation of hemorrhagic shock in trauma, whole blood transfusion had been forgotten as a therapeutic possibility during the larger part of the 20th century. Owing to the successful military use of whole blood in the early 1990s, extending to the early 2000s, whole blood has resurfaced as a lucrative therapeutic option for civilian trauma in the early 2010s, with approximately 25 % of level I trauma centers in the United States using whole blood transfusions in 2020. However, a large part of the developed

world is still hesitant on the benefits of using whole blood both in prehospital and in-hospital trauma resuscitations, owing to the relative scarcity of high-quality evidence (especially randomized controlled trials) on its effectiveness and safety when compared to the current standard of care - blood component therapy. With recently published prospective studies demonstrating either noninferiority or marginal superiority of whole blood transfusion to blood component transfusion, interest in the use of whole blood has once again increased. This narrative review aims to present the history, technical aspect and current evidence for the use of whole blood in both the military and civilian trauma settings in a concise, succinct manner and inform the reader on the contexts and situations in which whole blood transfusion might provide the greatest benefit, both logistics and cost-wise and mortality-wise.

Key words: blood; blood transfusion; emergency medicine; emergency medical services; military medicine

Sažetak

Puna krv je bila prvi krvni pripravak koji je korišten za transfuziju u modernoj medicini, a široko se primjenjivala tijekom posljednjih mjeseci Prvog svjetskog rata. S razvojem terapije krvnim komponentama i uvođenjem intravenskih kristaloidnih otopina za početnu reanimaciju hemoragijskog šoka u traumi, transfuzija je pune krvi bila gotovo zaboravljena kao terapijska mogućnost tijekom većeg dijela 20. stoljeća. Zahvaljujući uspješnoj vojnoj primjeni pune krvi od ranih 1990-ih do početka 2000-ih godina, transfuzija pune krvi ponovno je postala terapijska opcija u civilnoj traumatologiji početkom 2010-ih, a oko 25 % trauma centara razine I u Sjedinjenim Američkim Državama koristilo ju je u 2020. godini. Ipak, velik dio razvijenog svijeta i dalje je skeptičan prema prednostima primjene cijele krvi u izvanbolničkoj i bolničkoj reanimaciji bolesnika s traumom, ponajprije zbog relativnog nedostatka visokokvalitetnih dokaza (osobito randomiziranih kontroliranih studija) o njezinoj učinkovitosti i sigurnosti u usporedbi s standardom skrbi

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– terapijom krvnim komponentama. Uz nedavno objavljene prospektivne studije koje pokazuju jednako dobre ili bolje ishode s transfuzijom pune krvi u odnosu na transfuziju krvnih komponenti, interes za primjenu pune krvi ponovno je porastao. Ovaj pregledni članak ima za cilj prikazati povijest, tehničke aspekte i aktualne dokaze o primjeni cijele krvi u kontekstu vojne i civilne traume na sažet i jasan način te informirati čitatelja o okolnostima i situacijama u kojima transfuzija cijele krvi može pružiti najveću korist – kako s logističkog i financijskog aspekta, tako i u pogledu smrtnosti.

Ključne riječi: hitna medicina; hitna medicinska služba; krv; transfuzija krvi; vojna medicina

Introduction

History of whole blood transfusion

Whole blood was historically the first type of blood product transfused to patients in order to prevent or treat hypovolemic shock caused by hemorrhagic trauma. During World War I, a physiologist named Walter Cannon laid out a theory on the mechanism of hypovolemic shock and proposed whole blood transfusion as a potentially effective intervention for its prevention (1). The theories of Cannon and several other authors were considered sensible enough to implement citrated whole blood transfusions by the United States Army during the final months of World War I (2). Since the first instances of whole blood transfusions, there were logistical limitations to their usage: during World War I, citrated whole blood was stored in Robertson bottles, filled with glucose, which enabled a maximum of 5 days of storage time before the glucose ran out and the quality of the whole blood declined (2). During World War II, this limitation was removed with the advent of Baxter bottles, which contained acid citrate dextrose - a solution which could be autoclaved, extending the safe and sterile storage time of whole blood to approximately 21 days (3). Further safety of blood transfusions was enabled by the implementation of plastic bags instead of Baxter bottles as the principal containers of blood products. Plastic bags, unlike bottles, were less prone to breaking and could withstand the high flow velocities during emergency transfusions with a lower incidence of air embolism (4). With time, owing to the advantages of using plastic bags for blood storage and the advent of technologies that allowed for the separation of whole blood into individual components (red blood cells, plasma and platelets), component therapy overtook whole blood transfusion as a primary treatment modality for hemorrhagic shock. During the Vietnam War, owing to the aforementioned logistical difficulties related to storage of whole blood, as well as a perceived high incidence of post-transfusion hepatitis, whole blood and blood component transfusions were replaced by intravenous crystalloid fluid therapy in the management of hemorrhagic shock. Further encouraged by the experimental work of Shires et al. (5), resuscitation of patients with hemorrhagic shock using primarily crystalloid infusions (with a ratio of infused crystalloid fluid volume to transfused blood product volume of 3:1) was recommended not only for military purposes, but also for civilian trauma management, finding its way into the first Advanced Trauma Life Support (ATLS) guidelines (6). However, these recommendations were often misapplied, which resulted in patients receiving up to 10 liters of intravenous crystalloids before being administered any blood products, leading to renal failure, interstitial edema, acute respiratory distress syndrome (ARDS) and, most importantly, severe coagulopathy. Miller at el. observed an increased bleeding tendency in patients receiving massive transfusions in the Vietnam War, successfully reduced by the administration of whole blood instead of crystalloids (7). During the 1980s and early 1990s, ATLS guidelines became the norm for the management of civilian trauma. Therefore, the strategy for the management of hemorrhagic shock in trauma suggested by the guidelines - administration of a 2 liter initial bolus of intravenous crystalloid fluids followed by administration of red blood cells and subsequent administration of plasma and/or platelets if the bleeding persisted, was the dominant treatment strategy during the aforementioned time period (4). The paradigm began to change in 1993, owing to a shark attack in Mogadishu, Somalia.

The shift in trauma care began in 1993, as emerging evidence pointed to the potential benefits of reintroducing whole blood transfusion.

Due to a shortage of blood component products, a US Army medical team stationed in Mogadishu opted for collection and use of whole blood for the treatment of a shark attack victim with bilateral lower extremity amputations. A stockpile of 120 units of whole blood was gathered and stored and was subsequently crucial in early resuscitation of military personnel during the Battle of Mogadishu, which occurred exactly 30 days following the shark attack incident (8). Following the battle, a review of the trauma resuscitation protocols endorsed by the US Army was conducted and use of whole blood transfusions was recommended by the Army's "Emergency War Surgery" manual (9). Following these changes, whole blood resurged as a standard of care during the war in

Iraq. In 2004, US Army forces stationed in Baghdad began using ABO type-specific whole blood for the resuscitation of traumatic hemorrhage and found a higher success rate of reversing shock and coagulopathy compared to component therapy with red blood cells and plasma. Following their experience, a massive transfusion guideline was developed, recommending whole blood transfusion as first line therapy for hemorrhagic traumatic shock, with the transfusion of blood components (packed red blood cells, platelets and plasma) in a 1:1:1 ratio allowed until whole blood is available (10). In 2011, Nessen et al. published data from the war in Afghanistan, demonstrating improved survival in hemorrhagic shock patients receiving warm fresh whole blood when compared to those receiving blood component therapies (11). This and other publications led to the inclusion of whole blood transfusion as a viable resuscitation strategy for hemorrhagic shock in combat situations in the 2014 Tactical Combat Casualty Care (TCCC) guidelines (12).

The early 2010s also marked the advent of whole blood transfusion in the context of civilian trauma resuscitation. In 2011, owing to collaboration between the North Atlantic Treaty Organization (NATO) and the Norwegian Naval Special Operations Command (NNSOC), a research network was established, with the goal of investigating optimal strategies for the treatment of trauma in austere, challenging or resource scarce environments. The research network was named THOR - Trauma Hemostasis and Oxygenation Research.

It is important to note that, when discussing "whole blood" as a concept, there are three different modalities of its storage and use: warm fresh whole blood, cold fresh whole blood and cold stored whole blood. More detail on these is provided in the "technical aspects of whole blood collection, storage and transfusion" paragraph. In the paragraphs regarding the evidence for use of whole blood, the type of whole blood according to storage method is defined for each individual study, as well as the information if the whole blood used was low-titer type O or ABO type-specific. This research network focused on applying concepts acquired and tested in the context of combat casualties to civilian trauma, publishing a protocol on the collection and prehospital use of whole blood in austere environments (13). The group also published literature reviews and their own retrospective data on the safety of transfusing low-titer type O Rh positive whole blood with regards to isoimmunization (14). Following the efforts of the THOR group, other researchers started investigating the use of whole blood in civilian trauma more intensively, yielding a wealth of studies that shall be discussed and presented in the "evidence for the use of whole blood for civilian trauma management" paragraph of this manuscript.

The aim of this narrative literature review is to evaluate and present the evidence on the efficiency and safety of using whole blood transfusion for the management of hemorrhagic shock, with a major focus on hemorrhage caused by traumatic injury, while also providing a technical background and information essential to understanding the nuances of whole blood transfusions.

The authors deem a cohesive narrative literature review with a primarily educational goal and structure necessary, as current research has demonstrated that, while whole blood transfusion has been accepted by the emergency medicine community in recent years, its implementation is mostly nominal. According to data from 2020, approximately 1 in 4 level I trauma centers in the United States use whole blood transfusions for the resuscitation of traumatic hemorrhagic shock (15). According to a study by Hanna et al, who conducted a nationwide analysis of whole blood use in civilian trauma in the United States, only a small fraction of patients with traumatic hemorrhagic shock receive whole blood transfusions in the first 24 hours in addition to blood component transfusions (280 of 8494 or just 3.3 % of patients in their study). Furthermore, of the 280 patients that received whole blood transfusions, 266 received only 1 unit of whole blood and 14 received 2 units of whole blood (16).

Although whole blood transfusion is increasingly recognized as a superior approach for hemorrhagic shock, its adoption in civilian trauma care remains limited and inconsistently implemented.

This data demonstrates extreme caution and hesitation in the use of whole blood transfusions for civilian trauma, despite the nominal implementation rate of 25 % among the level I trauma centers.

Therefore, this article may serve as a succinct, educational and straightforward review of the available literature, with the aim of informing providers on the benefits, flaws, effectiveness and overall safety of using whole blood transfusions when compared to the current norm, which is blood component therapy.

Technical aspects of whole blood transfusion

Each year, countless patients rely on blood, blood components, and plasma derivatives to increase their chances of surviving trauma. As of 2019, the European Commission (EC) had reported data for 25 countries that collected more than 17 million donations of whole blood and blood components, such as red blood cells, plasma, and platelets. The collection of blood and plasma derivatives solely relies on human donors, making it a limited and invaluable resource. In numerous countries, whole blood (WB) collections form the fundamental pillar of the blood supply system (17). Ensuring an adequate

supply of blood, blood components, and plasma for patients in need of transfusions, while maintaining safety standards and preventing the transmission of infectious diseases, is a top priority for national health authorities, such as the European Commission (EC), Food and Drug Administration (FDA), European Directorate for the Quality of Medicines & HealthCare (EDQM) and other (18). Every nation encounters obstacles in establishing a sustainable and adequate supply of blood and blood products, all the while maintaining the highest standards of quality and safety. These efforts are crucial to address both well-known and emerging threats to public health. Current practice in civilian aspects is that whole blood transfusion is not indicated when component-specific treatment is available, such as using red blood cells to treat anemia or using fresh frozen plasma to treat coagulopathy in trauma (19). Initiating early blood transfusion and implementing massive transfusion protocols (MTP) in the prehospital setting can effectively prevent the development of coagulopathy. By administering blood products promptly, this proactive approach aims to address coagulation issues at an early stage, ensuring better outcomes for patients (20).

Ensuring a safe and sufficient blood supply is a global challenge, while early transfusion leads to better trauma outcomes.

On the other hand, Black et al. stated that in both out-of-hospital and deployed hospital settings, the United States military has adopted whole blood as a standard of care. Recent studies in civilian contexts also indicate an increasing use of whole blood as an alternative approach to trauma resuscitation, moving away from conventional component therapy (21). Speaking about other advantages of WB, some of which will be considered: later in the paper, the following benefits should be considered simplified transfusion process, cost-effectiveness, balanced composition of blood components, improved coagulation, less complex storage requirements, veritable replication of blood lost by hemorrhage, fewer transfusion reactions (e.g Transfusion Related Acute Lung Injury, TRALI) (22-25).

The collection of whole blood is a critical procedure characterized by the need for standardization in order to prioritize safety and optimize efficiency. Donor eligibility is determined through comprehensive screening, considering medical history, health status, and potential risk factors. Ensuring informed consent is an ethical imperative, securing voluntary and willing participation from healthy donors – preferring those with blood type O, with a lower antibody titer (26). The systematic whole blood collection process commences with proper donor preparation, followed by venipuncture performed by skilled healthcare professionals. The collection phase typically spans 8-15 minutes, yielding approximately 450 - 500 milliliters of whole blood. Observed practice in existing studies is that 450 mL ± 10 % of WB is collected in bags containing a 1:7 ratio of anticoagulants to blood. (26-27). The types and impact of anticoagulants shall be explained later in this paragraph. In their publications, Siversten et al, Strandenes et al, Schubert et al and other authors had exclusively used FDA-approved blood bag systems containing a platelet sparing, whole blood leukoreduction filter - Imuflex WB-SP collection set, containing 70 mL of citrate-phosphate-dextrose (CPD) (28-30). Furthermore, an additional blood sample was obtained using blood collection K2- EDTA tubes from each donor to conduct baseline measurements of the complete blood count (CBC).

When discussion anticoagulants for whole blood, studies mostly mention citrate-phosphate-dextrose (CPD), which had already become the most frequently used anticoagulant for this purpose in the 1950s and still is despite the development of CPD supplemented with adenine (CPDA-1). Some articles mention citrate–phosphate-double dextrose (CP2D) as the anticoagulant of use, but it didn't take root in standard practice. The frequency of use and selection of a particular anticoagulant are dependent on its shelf life, in order to optimize the quality of stored whole blood. A comparison of the anticoagulants mentioned above was published by Meledeo et al in 2019, demonstrating a slight increase in clotting time measured by thromboelastography over time, irrespective of the anticoagulant-preservative solution used. However, the use of CPDA-1 resulted in a significantly longer storage time, up to 35 days, and CPD stored WB could be stored for a maximum of 21 days in the same storage conditions of 2 – 4°C (27). Currently, there is no commercially available collection set that includes an in-line platelet-sparing filter along with CPDA-1 as an additive. Dumont et al. discussed the factors taken into account when selecting an anticoagulant for whole blood, including the viability of red blood cells residing in whole blood with regards to shelf-time (31).

Thromboelastometry analyses were developed with the aim of detecting alternations in the coagulation status of blood samples, with its principles applicable to testing the hemostatic properties of stored WB. A point-of-care device utilizing rotational thromboelastometry (ROTEM) can provide analysis of the viscoelastic properties of whole blood samples, such as clot formation and dissolution (e.g. coagulopathy) (35). There is evidence that point-of-care ROTEM analysis can be performed under demanding operational conditions, with a relatively low rate of erroneous readings (36). Time to first clot formation (R), rate of clot formation (α), and maximum clot strength (MA) are the most commonly performed measurements when testing of the hemostatic properties of whole blood testing is concerned (30).

Leukoreduction (LR) is considered an additional measure that could enhance the safety of whole blood use. LR effectively lowers the risk of human leukocyte antigen

(HLA) alloimmunization, incidence of febrile reactions, and viral transmission. However, it was posited that leukoreduction might have an effect on the number and function of platelets inside whole blood. Pidcoke et al. observed a gradual decrease in the number of platelets during storage (37). Morris et al also observed the effects of preforming leukoreduction and found decreased platelet aggregation compared to non-leukoreduced (NLR) blood. However, performing leukoreduction at 4 hours following whole blood collection did not lead to a reduction in platelet function (28). Similar results were demonstrated in studies conducted by Remy et al and Sieltz et al, that showed delayed clot development, growth, and formation in LR WB over a 30-day time frame (38-39). It is possible to successfully perform leukoreduction by using the Imuflex WB-SB filter, which was prescribed by the FDA in 2012 (40).

Pidcoke et al. observed non-leukoreduced WB (NLR WB) stored at 4°C and found a 33 % decline in the number of platelets until the end of the viable storage period.

The rate of decline in platelet count in WB stored at 4°C was higher compared to WB stored at room temperature, but the overall clotting ability was maintained during the 21 day shelf life (37). A study by Slichter et al. performed on cold stored NLR WB showed a reduction in platelet count by 25 – 30 % during the 22-day shelf time (41).

During each transfusion, providers should be cautious of pathogens which are the cause of transfusion-transmitted infections. A major logistical challenge is the development of a method of pathogen inactivation (PI) methods that does not damage WB units. Leukodepletion (LD), or leukocyte depletion, is one of most important methods of PI used in order to reduce the risk of transmission of intraleukocytic pathogens (e.g., human T-lymphotropic virus type 1, prions, cytomegalovirus). There are WB LD filters commercially available for this purpose that achieve results adequate for meeting FDA requirements for both in vitro and in vivo evaluations (32). Other methods of PI include using riboflavin for the reduction of pathogen activity (33). Pidcoke et al. performed measurements of platelet numbers in WB after using

riboflavin and UV-B illumination for PI. They concluded that there is no significant difference between controls and WB treated with riboflavin and UV-B illumination (37).

However, a study by demonstrated a sharp decline in platelet count inside pathogen-reduced WB during storage, with platelet counts falling below 150 x $10^{\wedge 9}$/L from day 3 onwards (34).

Military and combat use of whole blood

Following the historical developments and the implementation and popularization of the use of whole blood transfusions in the setting of military trauma, more studies have been conducted in order to more precisely define the contexts in which whole blood may yield the most beneficial outcomes.

A case series by Fisher et al. described the accessibility and transportation possibilities of low titer group O whole blood in combat missions and feasibility of starting transfusion therapy at the point of injury. Out of 15 casualties described, only one patient died in the resuscitative surgical center and 2 died before arrival to hospital (42).

A retrospective study by Spinella et al. lowed two groups of hemorrhaging trauma patients in the military setting, the first of which received warm fresh whole blood + red blood cells + plasma and the second received red blood cells, plasma and apheresis platelets. 100 patients were analyzed in the first group and 254 in the second group. The group that received whole blood + red blood cells + plasma had an increased 24-hour (96 % vs 88 %, p = 0.018) and 30-day (95 % vs 82 %, p = 0.002) survival when compared to the second group (43).

A prospective study by Nessen et al. compared the outcomes of patients from US army forward surgical teams with and without use of fresh whole blood in addition to red blood cells and fresh frozen plasma. When the outcomes of patients who received massive blood transfusion (10 units of red blood cells or equivalent in fresh whole blood) were compared between the two groups, a significantly lower mortality rate was observed in patients who received fresh whole blood (8.16 % vs 26.67 % p = 0,025). Furthermore, there was no difference in mortality between patients who received unmatched type O fresh whole blood (6.7 %) versus type-specific fresh whole blood (6.1 %) (11).

Early fresh whole blood transfusion near injury sites improves survival in military trauma and shows promise for civilian use.

A retrospective review of combat casualties by Perkins et al. showed similar 4-hour and 30-day survival between patients who received fresh whole blood and those who received apheresis platelets. Patients who received fresh whole blood had also received less units of plasma (8 vs 12, p < 0.001) and cryoprecipitate (0 vs 10, p < 0.001). Also, a lower proportion of patients in the whole blood group received recombinant factor VIIa (55 % vs 70 %, p = 0.02). There was no significant difference in observed adverse events except for acute respiratory distress syndrome (ARDS), which was more common in the fresh whole blood group (18.8 % vs 7.4 %, p = 0.002) (44).

A large study (n=1111) by Gurney et al. compared patients who received fresh whole blood and those that did not, but had received at least one unit of red blood cells in Role 2 environments. Following an adjusted analysis, the authors found an increased association with mortality in critical patients who did not receive fresh whole blood [hazard ratio (HR) = 2.8; 95 % CI 1.2 – 6.4, p = 0.017] (45).

Whole blood transfusion in trauma may lower mortality, reduce additional blood product use, massive transfusions, and complications like transfusion related acute lung injury.

An important consideration for the use of fresh whole blood transfusions in the military setting is the potential reduction physical performance of whole blood donors following the donation process. Strandenes et al. tested physical performance of participants before and 2-6 minutes following the donation of 450 mL of whole blood. They reported no significant difference in physical performance test scores or VO2 max (46). Conversely, a randomized, double-blinded study by Eliassen et al. demonstrated a reduction in absolute VO2 max by 11.2 % ($p < 0.05$) and reduced exercise tolerance time for an average of 92 seconds ($p < 0.05$) when compared to baseline following donation of whole blood (47).

Another important question regarding the feasibility of using whole blood transfusions in the military setting is the effectiveness of its utilization and the rate of blood product waste. Vanderspurt et al. analyzed blood product utilization during US military operations in Iraq, Syria and Afghanistan. They found a utilization rate of 17.4 % for blood component products vs 14.3 % for low-titer O type whole blood (LTOWB), demonstrating no significant difference in utilization or waste rates between these two types of blood products (48).

Finally, it is important to note that in 2021, the Committee on Tactical Combat Casualty Care updated its guidelines on fluid therapy of hemorrhagic shock in combat settings, suggesting cold stored low-titer group O whole blood as preferred the resuscitation fluid for combat casualties, with the possibility of using fresh low-titer group O if cold stored LTOWB is not available (49).

The use of whole blood transfusions in the management of civilian trauma

As it was mentioned in the "introduction" paragraph, clinical investigations and considerations on using whole blood transfusion in the context of management of civilian trauma date back to 2011 and the establishment of the Trauma Hemostasis and Oxygenation Research (THOR) network, borne from the collaboration between the North Atlantic Treaty Organization (NATO) and the Norwegian Naval Special Operations Command (NNSOC). Following the establishment of the THOR network, medical investigators from two large countries (United States of America and Norway) diverted their attention to the efficiency, safety and possibilities of implementation of whole blood transfusions into their medical systems. Following the intensification of their research efforts and an increase in the interest regarding whole blood transfusions, a solid throughput of literature has been established. The most important studies researching the implementation of whole blood in the aforementioned medical systems shall be discussed in this paragraph.

Prehospital transfusion of blood or plasma within the first minutes post-injury can be a critical determinant of survival in hemorrhagic trauma.

Before discussing the literature, it is important to explain the two main environments in which whole blood may be implemented and the rationale for doing so. The first environment is the prehospital emergency service. A study by Shackelford et al. analyzed data on combat casualties of the United States Army in Afghanistan between 2012 and 2015. The authors analyzed data on patients who were evacuated from the point of injury and suffered either a traumatic limb amputation or traumatic hemorrhagic shock, defined by a systolic blood pressure < 90 mmHg or a heart rate > 120 beats per minute. Data on 502 patients was included in the final analysis and it was found that patients with traumatic hemorrhage who received prehospital blood product transfusions had a significantly lower rate of 30-day mortality when compared to patients who did not receive prehospital transfusions (11 % vs 23 %, $p = 0.04$). The hazard ratio for mortality in patients who received prehospital transfusions was 0.39 [95 % confidence interval (CI) 0.16-0.92, $p = 0.03$]. A reduced risk of mortality was observed in patients who received an initial blood product transfusion in 15 minutes or less following pickup from the point of injury by the medical evacuation vehicle (HR 0.17; 95 % CI 0.04-0.73, $p = 0.02$) (50). Pusateri et al. conducted a post-hoc analysis of the Prehospital Air Medical Plasma (PAMPer) and Control of Major Bleeding After Trauma (COMBAT) trials, both of which examined the effects of prehospital plasma transfusions on the mortality of patients with traumatic hemorrhagic shock. The analysis included 626 patients with a median age of 42 years and demonstrated a statistically significant reduction in mortality associated with prehospital plasma transfusion [hazard ratio (HR) 0.65; 95 % CI 0.47-0.90, $p = 0.01$] following adjustment for patient age and injury severity. Furthermore, patients who did not receive prehospital plasma transfusions had an increased risk of mortality (HR 2.12; 95 % CI 1.05-4.30, $p = 0.04$) if the duration of the transport to a hospital facility exceeded 20 minutes. There was no observed increase in mortality in relation to duration of prehospital transport in patients who received prehospital plasma transfusions (51). These studies demonstrate a significant mortality benefit to prehospital transfusions of blood products, especially if applied early during the prehospital transport or in situations where

transport takes longer than 20 minutes. Due to these time-sensitive requirements and conditions, whole blood, owing to its logistical simplicity of containing red blood cells, plasma and platelets in a single bag, presents as a compelling blood product of choice for the prehospital arena.

The feasibility of implementing whole blood in the prehospital setting was extensively studied by a group of Norwegian investigators. Bjerkvig et al. conducted a survey of 13 helicopter emergency medical services (HEMS) and 7 search and rescue (SAR) services in Norway regarding their blood product inventories and preferences for specific products or components (52). They found that 20 % of the services participating in the survey carried low titer group O whole blood as part of their regular blood product inventory. Among the services that did not have LTOWB as part of their regular inventory, 88 % expressed a desire to implement it in the future. The main challenges in obtaining and implementing LTOWB in the HEMS setting were lack of LTOWB donors, concerns of potential waste of blood products due to a low number of annual transfusions, lack of "hard" evidence on the efficiency of LTOWB in the HEMS settings and LTOWB not being available as a blood product in their local blood bank. The authors also surveyed the blood banks providing the HEMS services with LTOWB and found that blood product waste was indeed a significant problem, with half of the blood banks reporting a waste rate of > 75 %. One blood bank reported a waste rate of only 26.4 %, due to utilizing unused LTOWB returned by the HEMS services for in-hospital massive transfusions.

Another Norwegian study, by Sunde et al. analyzed data on prehospital transfusions from the HEMS base in Bergen during a period of 5 years (2015 - 2020). They found that 48 patients received LTOWB during the aforementioned period, with no severe adverse events, transfusion reactions or major logistical challenges reported. This study also demonstrated impressive efficiency of blood product use, with 0 instances of blood product waste reported during the 5 year period due to sending unused LTOWB units for in-hospital use (53).

Successful implementation of LTOWB in a prehospital system in the United States was described by Sayre et al, who reported their emergency medical ambulance service transfusing 51 units of LTOWB into 39 patients during a 1-year period, with an average cost of $ 1138 per patient transfused. The authors also reported no waste of blood products, as all of the units issued by the associated hospital were either used in the field or returned for in-hospital use (54). Levin et al. described the use of LTOWB for the management of traumatic hemorrhagic shock in Israel by the Israel

Defense Forces Airborne Combat Search and Rescue Unit. They reported transfusing 33 units of LTOWB to 27 patients over a 2,5-year period. However, their study also demonstrated the perils of using LTOWB in a system with a low incidence of transfusions and no developed program for the return of unused units of LTOWB for in-hospital use - the waste rate of LTOWB during the 2,5-year period was 98 %, due to the factors listed above (55).

The literature comparing prehospital administration of whole blood to blood component therapy with regards to patient important outcomes is relatively scarce. Williams et al conducted a prospective observational study of transfusion therapy in trauma patients both in the prehospital HEMS and the in-hospital emergency department. During a period of 8 months, they enrolled 350 patients who received either blood component therapy or LTOWB. While there was no difference in survival between patient groups in the unadjusted analysis, a significant association between survival and receiving LTOWB was found following adjustment for patient age, prehospital physiology and severity of injury [odds ratio (OR) 2.19; 95 % CI 1.01-4.76,; p = 0.047]. There was also a significant reduction in the need for blood product transfusions following initial management in the emergency department (ED) observed in the LTOWB group (OR 0.47; 95 % CI 0.23-0.94, p = 0.033) (56).

Braverman et al did a retrospective analysis of a single institution trauma registry, extracting data on patients who received prehospital blood product transfusions. Data on 538 patients was analyzed and the patients were divided into two groups: those who received prehospital LTOWB transfusions and those who received no transfusions in the prehospital setting. Patients who received prehospital LTOWB had a significantly lower rate of early mortality, defined as death in the trauma bay (0 % vs 7 %, p = 0.04) (57).

Braverman et al. recently conducted another registry analysis, extracting data from two level I trauma center registries and collecting data on patients who underwent transfusions. Data on 1562 patients was included in the analysis and the patients were divided into those who received prehospital LTOWB and those who did not. There were no significant differences in mortality or length of stay between groups. Patients who received prehospital LTOWB had a lower need for massive transfusion protocols (MTPs) (22.6 % vs 32.4 %, p = 0.01) (58).

The rationale for using whole blood in-hospital is based on the idea that whole blood is logistically simpler to collect, store and transfuse while also being potentially cheaper than blood component therapy. The logistical simplicity and straightforwardness of acquiring and using whole blood has led to several authors advocating for the use of whole blood in small rural hospitals, as well as designing protocols for the establishment of emergency whole blood donor pools, also called "walking blood banks", in rural areas that are underserved regarding the acquisition and transport of blood component products (59-60).

The volume of literature on whole blood in the emergency department or the trauma bay is significantly larger when compared to the literature on prehospital use of whole blood.

Most of the in-hospital data on the safety and efficiency of whole blood comes from the United States, where whole blood had begun to resurge as a viable blood product for transfusion therapy of hemorrhagic shock in trauma since 2016, when a number of trauma centers, including Mayo Clinic, implemented it in their protocols (61). However, one of the first studies on the effects of whole blood transfusion on mortality was conducted in Australia in 2011, when Ho et al compared the outcomes of patients requiring massive transfusion who received more than 10 packs of red blood cells to those who received warm fresh whole blood. They found 30-day or 8-year survival benefit associated with receiving whole blood (HR 1.05; 95 % CI, 0.41-2.65, p = 0.93) (62). One of the earliest studies on the effectiveness and safety of whole blood transfusions in the United States was a randomized controlled trial from 2013 conducted by Cotton et al (63). In the study, severly injured patients with traumatic hemorrhagic shock were randomized to receive either whole blood transfusions or red blood cells and plasma in a 1:1 ratio. Both groups received a unit of platelets for every 6 units of whole blood or red blood cells + plasma transfused. The primary outcome was the average transfusion volume received in each patient group and those were not significantly different amongst a total of 107 patients divided into two groups. However, following the exclusion of patients with traumatic brain injury from the analysis, the group randomized to whole blood transfusions received less units of red blood cells (median 3 vs 6, p = 0,02), plasma (4 vs 6, p = 0.02), platelets (0 vs 3, p = 0,09), and total blood products (11 vs 16, p = 0.02) during the 24-hour period following admission to the trauma bay.

Two more randomized controlled trials examining the effectiveness and safety of whole blood in the emergency department were planned: the Pragmatic Prehospital Group O Whole Blood Early Resuscitation (PPOWER) trial and the Evaluation of a Transfusion Therapy Using Whole Blood in the Management of Coagulopathy in Patients With Acute Traumatic Hemorrhage (T-STORHM) trial. The PPOWER trial was terminated in 2021 due to slow enrollment, financial considerations and the global COVID-19 pandemic (64), while the T-STORHM trial is still in the patient recruitment phase (65). Until the results of the T-STORHM trial are published, large prospective trials represent the highest quality of evidence available.

One of the largest prospective trials is a recent study conducted by the Shock, Whole Blood, and Assessment of Traumatic Brain Injury (SWAT) Study Group, enrolling 1051 patients with traumatic hemorrhagic shock from 7 different trauma centers (66). The results of the study demonstrated no significant difference in 4-hour, 24-hour or 28-day mortality between patients who received LTOWB and those who received blood component therapy. However, a subgroup analysis that included patients with an elevated prehospital probability of mortality demonstrated a significant reduction in risk of 4-hour [relative risk (RR) 0,52; 95 % CI 0,32-0,87, p = 0,01] and 28-day mortality (RR 0,70, 95 % CI 0,51 to 0,96, p = 0,03).

Other prospective trials include the one conducted by Siletz et al, comparing the effects of a combination of whole blood and blood component transfusion to transfusion utilizing only blood components on transfusion requirements of trauma patients with hemorrhagic shock (67). 60 patients in total were enrolled in the study, with the results showing no statistically significant difference in the average volume of transfusions received, mortality, complication rates or the number of intensive care unit or hospital-free days between groups.

Another prospective trial, published by Shea et al. compared the rates of survival between trauma patients with a requirement for massive transfusion who received LTOWB versus those who received blood component therapy transfusion. A total of 66 patients were enrolled in the study and the results demonstrated no significant difference in mortality between groups (21 % in the blood component group vs 16 % in the LTOWB group, p = 0.518). Following a multivariable logistic regression analysis, a significantly decreased risk of 24-hour mortality was found in patients who received whole blood transfusions (OR 0.81; 95 % CI 0.69-0.96, p = 0,017) (68). Similarly, a prospective observational trial by Duchesne et al. comparing outcomes between trauma patients with active hemorrhage who received whole blood transfusion versus those who received blood component therapy found no statistically significant association in the reduction of in-hospital mortality with receiving whole blood instead of blood components (HR 1.25; 95 % CI 0.60-2.58, p = 0.55). However, patients transfused with whole blood received significantly fewer units of red blood cells (p < 0.001) and plasma (p = 0.04) and also had a lower incidence of acute respiratory distress syndrome (ARDS) (p = 0.03), with significantly less days spent on mechanical ventilation (p = 0.03) (69).

A number of retrospective studies comparing whole blood to blood component therapy were also published, with most of them demonstrating no significant difference in mortality between groups (70-73) and some of them demonstrating a survival benefit associated with the use of whole blood when compared to blood component transfusion therapy (74-75).

Similar to prehospital application of blood product transfusions, time seems to be a relevant factor affecting clinically important outcomes in emergency department whole blood transfusions. A retrospective analysis of the American College of Surgeons' Trauma Quality Improvement Program (TQIP) database from 2017 to 2019

performed by Hosseinpour et al. found that transfusion of whole blood after more than 30 minutes following patient admission to the trauma bay was associated with an increased adjusted odds ratio of 24-hour mortality [adjusted odds ratio (aOR) 2.07, p = 0.015] and in-hospital mortality (aOR 1.79, p = 0.025), demonstrating the need for early application of whole blood in the resuscitation of traumatic hemorrhagic shock (76).

A meta-analysis by Crowe et al. synthesized the results of 12 studies comparing balanced blood component transfusion therapy to whole blood transfusion for the resuscitation of trauma patients and found no significant association of 30-day mortality with whole blood transfusions (OR = 0.79; 95 % CI 0.48–1.31) (77).

The results of the trials evaluating the effectiveness and safety of whole blood published until now and the trials comparing tranfusions of a 1:1:1 ratio of plasma, platelets and red blood cells to other ratios led to the Eastern Association for the Surgery of Trauma (EAST) to recommend the use of either blood component products transfused in a 1:1:1 ratio or whole blood for damage control resuscitation in patients with severe traumatic hemorrhage (78).

With the available literature comparing blood component therapy to whole blood transfusions demonstrating either no difference or a reduced mortality rate with the use of whole blood, another important question that arises is the cost-effectiveness of whole blood versus the current standard of care, i.e. blood component therapy. Based on the data from America's Blood Centers, a single unit of whole blood in 2017 cost $ 151,51, while the combined price of a single unit of red blood cells + fresh frozen plasma + platelets was $ 628,19 (79). A recent study by Ciaraglia et al. the comparing costs of LTOWB transfusion versus blood component transfusions found that the implementation of LTOWB transfusions reduced the mean annual cost for all blood products by 17.3 %. Furthermore, LTOWB tranfusions were significantly associated with a lower cost per patient and cost per patient per mL of transfused blood product when compared with blood component therapy at 4 hours, 24 hours and overall (p < 0.001) (80).

Conclusion

Whole blood transfusion for the treatment of hemorrhagic shock is a century-old concept that has resurged in recent years, attracting increased interest from trauma researchers. While the data for the effectiveness of whole blood transfusions in both the prehospital and hospital settings is relatively scarce, the available literature demonstrates either noninferiority or superiority of whole blood transfusions regarding mortality when compared to blood component transfusions. These results need to be tested in a well-designed, large multicenter randomized controlled trial in order to more definitely establish the role of whole blood in the resuscitation of traumatic hemorrhagic shock. In the case of more convincing positive evidence for its use surfacing in the future, the already lucrative concept of using whole blood (which, in addition to potential survival benefits offers logistical simplicity and cost-effectiveness) for trauma resuscitations may become more widespread and accepted, as current surveys on its use in the United States demonstrate a great degree of hesitance.

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PRIKAZ SLUČAJA / CASE REPORT

PLUĆA AUSKULTACIJSKI: PRETAKANJE

LUNG AUSCULTATION: BORBORYGMI

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Sažetak

Ileus označava mehanički poremećaj ili potpuni zastoj prolaska crijevnog sadržaja uslijed različitih patoloških stanja. Dijagnoza se postavlja klinički, potvrđuje radiološki, a liječenje najčešće uključuje kiruršku intervenciju. Ovdje prikazujemo slučaj bolesnice u dobi od 51 godine koja se prezentirala s nespecifičnim bolovima u epigastriju i neobičnim kliničnim statusom, te prikazujemo tijek njene obrade.

Ključne riječi: ileus; klinička dijagnoza; mehanička opstrukcija; nespecifični simptomi; radiološka dijagnostika

Abstract

Ileus is a condition characterized by a mechanical obstruction or complete cessation of intestinal content passage due to various pathological causes. Diagnosis is clinically established and confirmed through radiological imaging, with treatment often requiring surgical intervention. This case report presents a 51-year-old patient who presented with nonspecific epigastric pain and an atypical clinical presentation, highlighting the course of her diagnostic workup and management.

Key words: clinical diagnosis; epigastric pain; ileus; mechanical obstruction; nonspecific symptoms; radiological diagnostics

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Uvod

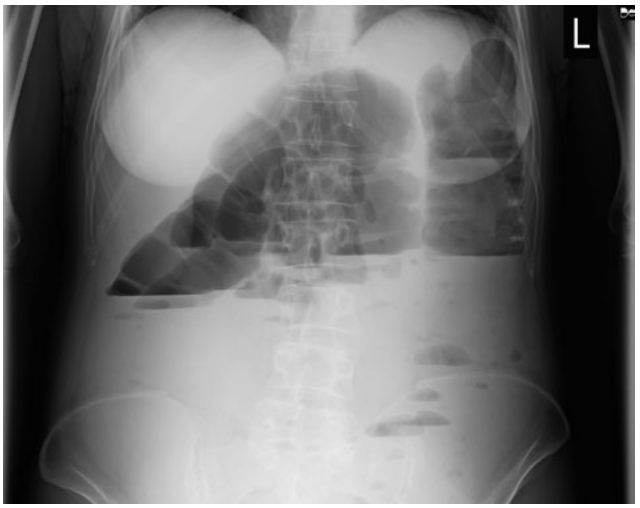
Ileus predstavlja klinički sindrom koji podrazumijeva djelomičnu ili potpunu mehaničku ili funkcionalnu opstrukciju crijeva, pri čemu dolazi do poremećaja fiziološkog prolaska crijevnog sadržaja. Takvo stanje najčešće se očituje nespecifičnim simptomima poput abdominalne boli, distenzije, mučnine, povraćanja te zastoja stolice i vjetrova. Sumnja na ileus najčešće se postavlja već tijekom početne kliničke obrade, temeljem detaljno uzete anamneze i kvalitetnog fizikalnog pregleda (1). U dijagnostičkom postupku ključnu ulogu imaju nativni rendgenski snimak abdomena te kompjuterizirana tomografija trbuha (engl. *multi-slice computed tomography*, *MSCT*), koji u većini slučajeva omogućuju potvrdu dijagnoze (1,2). U okviru terapijskog pristupa, rana konzultacija s abdominalnim kirurgom nerijetko je nužna, budući da se velik broj slučajeva ne može uspješno zbrinuti konzervativnim mjerama ili postoji visoki rizik od recidiva ukoliko se izostavi kirurška intervencija kada je ona indicirana (3). Cilj ovog prikaza slučaja je istaknuti koliko klinička prezentacija ileusa može biti nespecifična i naizgled neproblematična, unatoč potencijalno ozbiljnoj pozadini patološkog procesa.

Ileus je klinički sindrom s nespecifičnim simptomima, a pravovremena dijagnostika i rana kirurška konzultacija ključni su za uspješno liječenje.

Prikaz slučaja

Bolesnica, 51-godišnjakinja bez ranije poznatih kroničnih bolesti, javila se u hitnu medicinsku službu zbog povremenih epizoda jakih, tupih bolova u epigastriju u trajanju 3 dana. Bol je zračila prema donjim kvadrantima abdomena, nije bila povezana s unosom hrane, pogoršavala se u ležećem položaju, trajala je nekoliko sekundi te je spontano regredirala. Uz bolove je povremeno navodila mučninu, osjećaj pečenja u grlu, štucavicu, te je u dva navrata povratila želučani sadržaj bez tragova krvi. Defekacija je bila uredna, stolice su bile formirane, bez patoloških primjesa, a apetit očuvan.

Tijekom kliničkog pregleda, trbuh je bio mekan, difuzno blago osjetljiv na palpaciju u epigastriju, bez znakova organomegalije ili palpabilnih masa. Auskultacijski se bilježila uredna peristaltika. Međutim, auskultacijom pluća obostrano nad bazama zabilježeni su fenomeni nalik na pretakanje crijevnog sadržaja, što je pobudilo sumnju na prisutnost intratorakalne crijevne vijuge i moguću crijevnu opstrukciju.



Slika 1. Nativni RTG trbuha s prikazom distendiranih crijevnih vijuga i aerolikvidnih nivoa - visoki ileus.

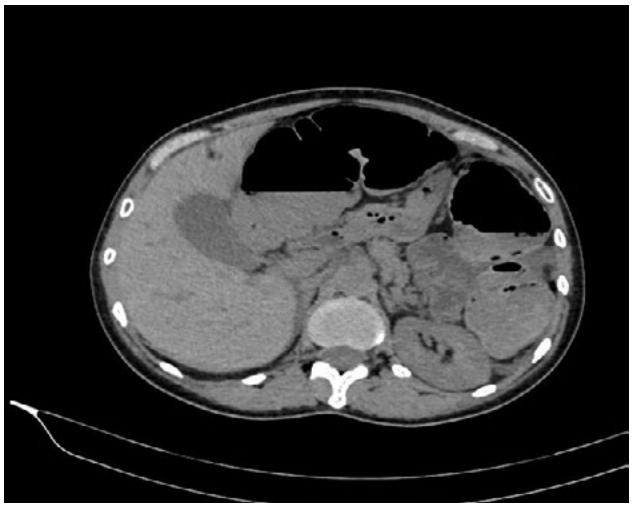
Nespecifični simptomi poput štucanja, pečenja u grlu, povraćanja želučanog sadržaja, te auskultacijskog nalaza pretakanja u prsima, mogu maskirati ozbiljne patološke procese poput ileusa, ističući važnost temeljitog pregleda i pravovremene dijagnostike.

Nativni snimak trbuha potvrdio je nalaz visoke opstrukcije tankog crijeva (tzv. visoki ileus) (Slika 1). Uvedena je nazogastrična sonda, kojom je odstranjeno približno 1000 ml crijevnog sadržaja, te je započeta nadoknada tekućine. Zbog nejasne etiologije opstrukcije, učinjen je MSCT trbuha, koji je pokazao infiltrativni stenozirajući proces u distalnom dijelu sigmoidnog kolona, uz sekundarni ileus tankog i debelog crijeva. Ujedno su bile vidljive hipervaskularne lezije u jetri, suspektne na metastatske promjene (Slika 2).

Bolesnica je hitno operirana. Učinjena je kolotomija s dekompresijom crijeva te resekcija sigmoidnog kolona po Hartmannu. Poslijeoperacijski oporavak protekao je uredno. Patohistološka analiza odstranjenog uzorka potvrdila je dijagnozu adenokarcinoma kolona. U daljnjoj dijagnostičkoj obradi potvrđena je prisutnost sekundarnih tumorskih lezija u jetri i plućima.

Rasprava

Ileus predstavlja klinički sindrom koji nastaje kao posljedica poremećaja normalnog prolaska crijevnog sadržaja kroz gastrointestinalni trakt, a klasifikacijom se dijeli na ileus tankog ili debelog crijeva (4). Etiologija je raznolika, pri čemu se najčešće radi o priraslicama nastalim nakon prethodnih abdominalnih zahvata, hernijama te neoplastičkim procesima (4,5).



Slika 2. MSCT trbuha s prikazom distendiranog tankog i debelog crijeva, aerolikvidnih nivoa i sekundarizama na jetri.

Na postavljanje kliničke sumnje najčešće upućuju simptomi poput bolova u trbuhu, mučnine, povraćanja, opstipacije i distenzije trbuha. Anamnestički podatci o prethodnim zahvatima u trbuhu, ranijim epizodama ileusa, zračenju trbuha ili zdjelice, upalnim bolestima crijeva te prisutnosti neoplazme dodatno usmjeravaju dijagnostički postupak (5,6). Fizikalni pregled može otkriti distenziju trbuha, hernijske otvore, poslijeoperacijske ožiljke ili palpabilne mase, dok auskultacija može ukazivati na odsutnost crijevne peristaltike ili pojavu zvuka pretakanja (6). Laboratorijska obrada korisna je u diferenciranju mehaničkog i funkcionalnog (paralitičkog) ileusa, osobito u prisustvu elektrolitskih poremećaja. Radiološka obrada, prvenstveno nativna radiografija trbuha i MSCT, imaju ključnu ulogu u potvrdi dijagnoze jer omogućuje prikaz distenzije crijevnih vijuga, aerolikvidnih nivoa te otkrivanje potencijalnog uzroka opstrukcije (7).

Liječenje ovisi o etiologiji i težini kliničke slike, a pristup može biti konzervativan ili kirurški (4,8). Konzervativni postupci uključuju zabranu peroralnog unosa hrane i tekućine, postavljanje nazogastrične sonde, infuzijsku nadoknadu tekućine, korekciju elektrolita, dekompresiju rektuma, prekid lijekova koji mogu pogoršati peristaltiku te mobilizaciju bolesnika. Ukoliko konzervativna terapija ne dovodi do poboljšanja ili postoji sumnja na organski uzrok, nužno je pravovremeno kirurško zbrinjavanje (8).

Ileus, zbog široke etiologije i nespecifičnih simptoma, zahtijeva preciznu dijagnozu i rano uključivanje kirurga za bolji ishod liječenja.

Prikazani slučaj dodatno naglašava važnost temeljitog kliničkog pregleda i pažljive interpretacije nespecifičnih simptoma. Naime, bolesnica bez ranije medicinske anamneze prezentirala se sa simptomima koji su početno mogli sugerirati na funkcionalne poremećaje (dispepsija, žgaravica, štucanje), dok je auskultacijski nalaz pretakanja nad bazama pluća bio ključan za sumnju na ileus. Radiološka obrada otkrila je visoki ileus kao posljedicu opstruktivnog tumora sigmoidnog kolona s već prisutnim sekundarizmima, čime je potvrđena važnost sveobuhvatnog pristupa dijagnostici. Brza kirurška intervencija omogućila je stabilizaciju stanja, no patohistološki nalazi i diseminacija bolesti ukazali su na već uznapredovali maligni proces.

Zaključak

Ovaj slučaj ističe važnost sveobuhvatnog kliničkog pregleda i pravovremenog korištenja radioloških metoda u postavljanju dijagnoze ileusa, koji može biti uzrokovan ozbiljnim patološkim stanjima poput malignih bolesti. U ovom slučaju, auskultacijski nalaz pretakanja i radiološke metode omogućile su pravovremeno prepoznavanje opstrukcije izazvane tumorom sigmoidnog kolona, dok su patohistološki nalazi i diseminacija bolesti ukazali na uznapredovali maligni proces. Ovaj prikaz slučaja potvrđuje značaj ranog prepoznavanja i brzog kirurškog zahvata, koji može značajno poboljšati ishode, unatoč uznapredovaloj bolesti.

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CASE REPORT / PRIKAZ SLUČAJA

MALIGNA STENOZA DUŠNIKA KAO UZROK STRIDORA – PRIKAZ SLUČAJA

MALIGNANT TRACHEAL STENOSIS AS A CAUSE OF STRIDOR – A CASE REPORT

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Sažetak

Uvod: Stridor je klinička manifestacija stenoze dušnika najčešće povezana s zatajenjem disanja. Zahtjeva hitno medicinsko zbrinjavanje dišnog puta te istovremeno žurno razrješenje etiologije i planiranje liječenja. Stenoza može biti posljedica benignih ili malignih bolesti, pri čemu se češće javlja kao dio diseminacije malignih bolesti drugih sijela, a rjeđe kao posljedica primarnih karcinoma dušnika.

Prikaz slučaja: Bolesnik star 26 godina, zaprimljen je u hitnu medicinsku službu zbog stridoroznog disanja. Učinjenom obradom dokazana je maligna neoplazma dušnika sa suženjem lumena na 3 mm. Zbog kritične stenoze dušnika bolesnik je bio intubiran, a interventnom bronhoskopijom učinjena je dilatacija traheje balonima uz postavljanje endotrahealnog stenta. Nakon zahvata bolesnik je bio hemodinamski i respiracijski stabilan te je nastavljeno liječenje kemoradioterapijom.

Zaključak: Stridor uzrokovan centralnom malignom opstrukcijom dušnika hitno je stanje koje početno zahtjeva zbrinjavanje dišnog puta s ciljem postizanja respiracijske stabilnosti. Nakon određivanja etiologije i stadija maligne opstrukcije, interventna bronhoskopija, uz mogućnost postavljanja stenta ukoliko je potrebno, predstavlja palijativnu terapijsku opciju s ciljem osiguravanja prohodnosti dišnih puteva.

Ključne riječi: bronhoskopija; neoplazme; stridor

Abstract

Introduction: Stridor is a clinical manifestation of tracheal stenosis, most commonly associated with respiratory failure. It requires urgent airway management along with rapid identification of the underlying cause and treatment planning. Tracheal stenosis may result from benign or malignant conditions, more frequently occurring as part of metastatic spread from malignancies of other sites, and less commonly as a consequence of primary tracheal cancers.

Case Presentation: A 26-year-old male patient was admitted to the emergency department due to stridorous breathing. Further diagnpostics revealead a malignant tracheal neoplasm with tracheal lumen being only 3 mm in diameter. Due to critical tracheal stenosis, the patient was intubated, and interventional bronchoscopy was performed with balloon dilation and placement of an endotracheal stent. After the procedure, the patient was hemodynamically and respiratorily stable, and treatment was continued with chemoradiotherapy.

Conclusion: Stridor caused by central malignant tracheal obstruction is a medical emergency that initially requires airway management to achieve respiratory stability. Once the etiology and stage of the malignant obstruction are determined, interventional bronchoscopy, including stent placement if necessary, represents a palliative treatment option aimed at maintaining airway patency.

Key words: bronchoscopy; neoplasms; stridor

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Uvod

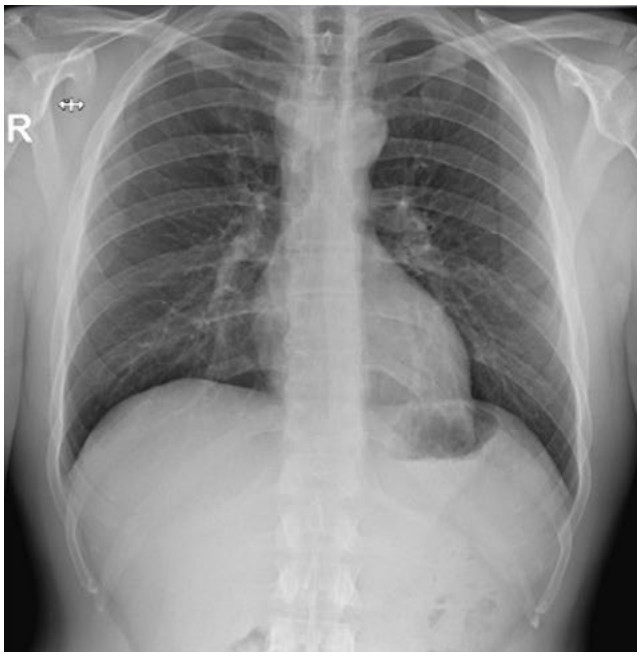
Maligna opstrukcija centralnih dišnih puteva definira se kao značajno i simptomatsko suženje dušnika, glavnih bronha ili intermedijarnog bronha uzrokovano neoplastičnim procesom. Nastaje kao posljedica lokalnog prodora tumora iz okolnih anatomskih struktura, vanjske kompresije okolnih struktura, metastatskog širenja tumora te, rjeđe, primarnih endobronhalnih neoplazmi (1). Ovisno o mehanizmu nastanka, opstrukcije centralnih dišnih puteva klasificiramo kao ekstraluminalne (ekstrinzična), endoluminalne (intrinzična) ili mješovite (kombinacija intrinzične i ekstrinzične komponente). Primarni tumori dušnika kao uzrok malignih opstrukcija velikih dišnih puteva su izuzetno rijetki, s učestalošću od 0,142 na 100 000 stanovnika godišnje (2). Epidemiološka analiza provedena na 578 slučajeva primarne maligne bolesti dušnika ukazala je veću učestalost u muškaraca (55 %) s predominantno histološkom slikom planocelularnog karcinoma (45 %) slijede adenoidni cistični karcinom (16,3 %) te karcinom koji nije drugačije specificiran (engl. *not otherwise specified, NOS*) ili nediferencirani karcinom (12,8 %) (3). Većina tumora dušnika zapravo su sekundarne endotrahealne metastaze koje nastaju izravnim prodorom iz susjednih organa ili hematogenim širenjem (4).

Maligna opstrukcija centralnih dišnih puteva zahtijeva hitno liječenje zbog mogućeg akutnog zatajenja disanja i stridora.

Klinička prezentacija tumorske opstrukcije dušnika ovisi o veličini endoluminalne komponente, smještaju, histološkom tipu i obrascu rasta tumorske mase. Opstrukcija koja uzrokuje suženje promjera dušnika na < 8 mm može dovesti do dispneje pri naporu, dok suženje < 5 mm uzrokuje dispneju u mirovanju (5). Uz dispneju, česti simptomi su kašalj, hemoptiza, zviždanje (engl. *wheezing*) i stridor (6). Stridor je simptom koji je najčešće povezan s akutnim zatajenjm disanja te zahtjeva hitno zbrinjavanje dišnog puta kao i žurno istovremeno razrješenje etiologije stridora kao i planiranje liječenja.

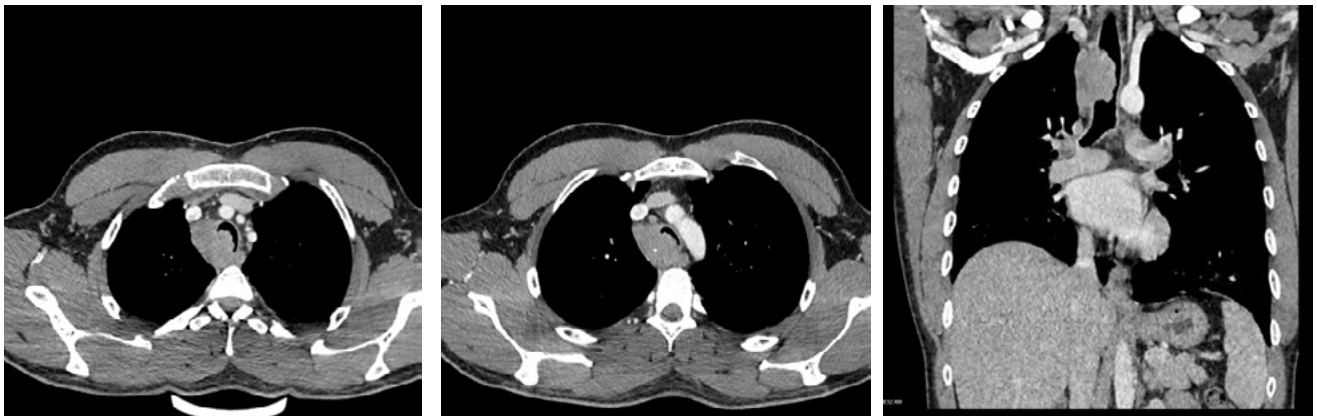
Prikaz slučaja

Muškarac, star 26 godina, bez značajnije osobne anamneze, unazad mjesec dana praćen je zbog zaduhe i „sviranja" u prsima. Početni RTG prsnog koša (Slika 1) i spirometrija bili su uredni. Terapija antitusicima i inhalacijskim glukokortikoidima nije dovela do povlačenjem simptoma, a klinička slika se dodatno pogoršala pojavom povišene temperature i stridoroznog disanja. Kontrolnim RTG-om prsnog koša utvrđena je lijevostrana upala pluća, nakon čega je bolesnik primljen na bolničko liječenje. Daljnjom obradom višeslojnom kompjutoriziranom tomografijom (engl. *Multislice Computed Tomography, MSCT)* vrata i



Slika 1. Početni RTG prsnog koša

prsišta otkrivena je tumorska tvorba u medijastinumu dimenzija 5,5 x 3,7 x 5,8 cm s infiltracijom dušnika i suženjem lumena na 3 mm (Slika 2). Zbog pogoršanja respiracijske funkcije uslijed kritične stenoze dušnika bolesnik je intubiran i priključen na strojnu ventilaciju. Fiberbronhoskopijom je utvrđeno suženje traheje u dužini od 55 mm u distalnom segmentu uslijed ekstramuralne kompresije stražnje stjenke s nekrotičnom, infiltriranom površinom koja kontaktno krvari. Uzeti su uzorci za patohistološku analizu te je postavljena dijagnoza karcinoma dušnika nemalih stanica (slabo diferencirani karcinom). Zbog dužine stenoze kirurško liječenje nije bilo moguće pa je indicirana interventna bronhoskopija sa svrhom rekanalizacije dušnika i ugradnje endotrahealnog stenta. Suženje je prošireno dilatacijskim balonima (dilatacijski balon kateter, Rusch i CRE Pulmonary Dillatattion Catether, Boston Scientific) nakon čega je postavljen endotrahealni hibridni stent dimenzija 20 x 60 mm (Microtech) (Slika 3). Nakon ugradnje stenta učinjen je kontrolni MSCT vrata i prsnog koša (Slika 4). Nakon postavljanja stenta bolesnik je bio hemodinamski i respiracijski stabilan, dobrog općeg stanja te je po prispijeću patohistološkog nalaza, na prijedlog multidisciplinarnog tima za tumore pluća započeto liječenje kemoradioterapijom zbog lokalno uznapredovalog karcinoma dušnika. Primijenjeni su paklitaksel i karboplatina uz ukupnu dozu zračenja od 60 Gy u 30 frakcija. Kontrolnim inspekcijskim bronhoskopijama nakon postavljanja stenta uočene su nekrotične promjene i granulacije uz donji, te flotirajuće fibrozne membrane uz gornji rub stenta koje su uklonjene elektroomčom i elektroresekcijom. Nakon dovršetka onkološkog liječenja ovisno o lokalnom bronhoskopskom nalazu planira se vađenje ili zamjena stenta.



Slika 2. MSCT vrata i prsnog koša: tumorska tvorba gornjeg medijastinuma veličine 5,5 x 3,7 x 5,8 cm s infiltracijom dušnika i suženjem lumena na 3mm

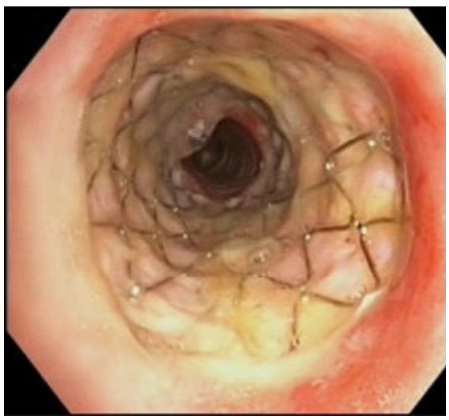
Diskusija

Zbog nespecifičnih simptoma stenoza traheje, često ostaje neprepoznata sve do razvoja kritičnog suženja, što je osobito izraženo kod bolesnika kod kojih dijagnoza tumora još nije postavljena. Takvi se bolesnici često liječe zbog drugih, učestalijih uzroka dispneje i sviranja u prsima, poput astme i kronične opstrukcijske bolesti pluća (KOPB) (7). To je bio i slučaj i kod našeg bolesnika, koji je prethodno liječen inhalacijskom terapijom zbog sumnje na astmu. U liječenju maligne opstrukcije centralnih dišnih puteva bronhoskopske metode imaju ključnu ulogu jer omogućuju brzo i učinkovito zbrinjavanje akutnih simptoma u skladu s kliničkim stanjem bolesnika One uključuju termalne ablativne tehnike, kriorekanalizaciju i krioterapiju, dilataciju, postavljanje stenta te mehaničko uklanjanje tumorske mase. Dok kirurško liječenje, kemoterapija i radioterapija predstavljaju dugoročne terapijske opcije, bronhoskopske intervencije u području centralnih dišnih puteva, osim u rijetkim kurativnim slučajevima, primarno su palijativnog karaktera, s ciljem osiguravanja prohodnosti dišnog puta i poboljšanja respiracijskog statusa bolesnika.

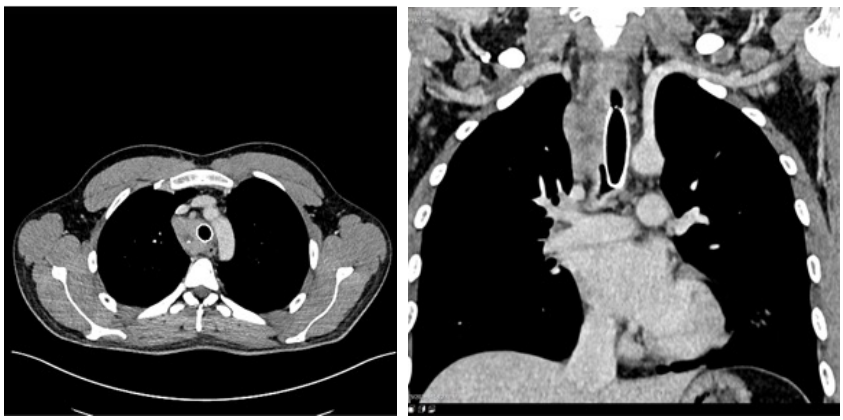
Bronhoskopija je ključna dijagnostička i terapijska metoda u hitnom liječenju akutne maligne opstrukcije dišnih putova, koja omogućava brzo poboljšanje respiracijske funkcije bolesnika.

Uspjeh bronhoskopskih rekanalizacija dišnih puteva postiže se u većine bolesnika te iznosi do 90 % (8-10). Unatoč izrazito visokoj stopi tehničke uspješnosti bronhoskopske rekanalizacije, komplikacije nisu rijetkost. Analiza podataka iz studije koja je obuhvatila 554 terapijske bronhoskopske intervencije pokazala je učestalost komplikacija od 19,8 % (11). Studija je uključila bolesnike s benignim i malignim stenozama velikih dišnih puteva, pri čemu je učestalost komplikacija bila veća kod malignih uzroka (25 %). Najčešće komplikacije bile su hipoksemija, pneumotoraks, potreba za intenzivnijim nadzorom, krvarenje i hipotenzija. Ukupna 30-dnevna smrtnost iznosila je 7,8 % (11). Budući da stent ne djeluje na tumorsku masu, njegova uloga je prvenstveno palijativna, s ciljem ublažavanja simptoma opstrukcije dišnog puta, poboljšanja općeg stanja bolesnika i primjene ciljane onkološke terapije. U slučajevima ekstrinzične kompresije, stent predstavlja jedinu metodu koja dugoročno može održavati prohodnost dišnog puta. Suprotno tome, kod bolesti koje zahvaćaju isključivo unutrašnji lumen dišnog puta, stent se najčešće ne koristi kao terapija prvog izbora. Dimenzije stenta trebaju biti pažljivo odabrane kako bi se izbjegle komplikacije poput granulacija i ishemije sluznice uslijed prevelikog promjera, odnosno migracije stenta i potencijalne asfiksije ako je promjer nedovoljan (12). Budući da tijekom onkološkog liječenja može doći do promjena u lokalnom statusu, iznimno je važno osigurati redovito kliničko praćenje bolesnika i kontrolu pozicije stenta kako bi se na vrijeme prepoznale i spriječile eventualne komplikacije. Ost i suradnici proveli su istraživanje komplikacija povezanih s postavljanjem stenta kod malignih bolesnika. Analizirano je 195 postupaka ugradnje stenta na 172 bolesnika. Najčešće komplikacije bile su respiracijska infekcija povezana sa stentom, koja je zahtijevala hospitalizaciju u 23 % slučajeva (73 bolesnika), te migracija stenta zabilježena u 27 od 163 analizirana slučaja (13).

Kod prikazanog bolesnika, stent postavljen u dušniku bio je obložen gnojnim naslagama, a distalno ispod stenta bile su prisutne granulacije. Kako bi se spriječila pojava naslaga na stentu preporuča se redovita primjena inhalacija fiziološke otopine (14), dok se pojava granulacija najčešće rješava dilatacijom ili



Slika 3. Prikaz endotrahealnog stenta



Slika 4. Kontrolni MSCT vrata i prsnog koša nakon ugradnje stenta: Vidi se tumorska tvorba u gornjem medijastinumu paratrahealno desno dimenzija 48 x 39 x 61 mm. Tumor je djelomično nekrotičan i vidi se manji kalcifikat centralno. Infiltrira i okružuje dušnik te je neodvojiv od paratrahealnih limfnih čvorova.

elektrokoagulacijom, što se pokazalo učinkovitom terapijom i kod našeg bolesnika (15).

Zaključak

Stridor uzrokovan centralnom malignom opstrukcijom hitno je stanje koje zahtjeva brz i koordiniran multidisciplinarni pristup s ciljem stabilizacije bolesnika i osiguranja prohodnosti dišnog puta. Iako se početno može primijeniti intubacija endotrahealnim tubusom kao metoda prve linije, nakon utvrđivanja etiologije i stadija opstrukcije, interventna bronhoskopija postaje ključna palijativna terapijska opcija kod inoperabilnih slučajeva. Ova metoda omogućuje različite tehnike rekanalizacije dišnih puteva, a u slučaju tumora s pretežno ekstramuralnom ili kombiniranom opstrukcijom, uključuje i postavljanje stenta.

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