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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.

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CONTENT

ANNALES MEDICINAE URGENTIS: *MESSAGE FROM THE EDITORS*

Prof. Višnja Nesek Adam, MD, PhD

Prof. Ivan Gornik, MD,PhD

Dear Colleagues,

It is our great pleasure to present the fifth issue of *Annales Medicinae Urgentis*. With each new issue, we continue to pursue our mission of publishing high-quality, scientifically sound, and clinically relevant articles that contribute to the advancement of emergency and critical care medicine and to the improvement of patient care.

We are particularly pleased that, in addition to original scientific articles, review papers, and case reports, this issue also features the best papers by young colleagues awarded at the 7th Congress of Emergency Medicine. Their publication reflects our commitment to recognizing and encouraging excellence, supporting the development of the next generation of authors, and providing young physicians and healthcare professionals with the opportunity to share their knowledge and experience with the wider professional and scientific community.

This fifth issue also marks an important milestone in the development of our journal. Over the past year, *Annales Medicinae Urgentis* has significantly expanded its international visibility through its inclusion in several recognized bibliographic and scholarly databases, including ROAD (Directory of Open Access Scholarly Resources), Google Scholar, Hrčak, OpenAlex, Dimensions, Scilit, and J-Gate. This indexing enhances the accessibility, discoverability, and international recognition of the articles published in our journal, while confirming the continuous efforts of the Editorial Board, authors, and reviewers to maintain and further improve the journal's scientific quality and publishing standards.

We would like to express our sincere gratitude to all authors for their trust, to our reviewers for their expertise, dedication, and invaluable contribution, and to the members of the Editorial Board and all collaborators whose commitment enables the continuous development of the journal. We would also like to extend our special appreciation to the young authors whose award-winning papers from the 7th Congress of Emergency Medicine have enriched this issue with their enthusiasm, knowledge, and professional dedication.

We hope that the articles published in this fifth issue will prove valuable in everyday clinical practice, inspire further professional and scientific work, and strengthen the position of *Annales Medicinae Urgentis* as a respected journal in the field of emergency medicine.

Thank you for your continued trust and support. We warmly invite you to contribute your future work and join us in the ongoing development of *Annales Medicinae Urgentis*.

Warm regards,

Prof. Višnja Nesek Adam, MD, PhD
and Prof. Ivan Gornik, MD,PhD

Editors-in-Chief, Annales Medicinae Urgentis

ORIGINAL ARTICLE / IZVORNI ZNANSTVENI ČLANAK

RESPIRATORY DEPRESSION IN COMATOSE ALCOHOL-INTOXICATED PATIENTS: IMPACT OF CO-INGESTION AND AIRWAY MANAGEMENT – A 36-MONTH RETROSPECTIVE COHORT STUDY

RESPIRACIJSKA DEPRESIJA U KOMATOZNIH BOLESNIKA S AKUTNOM INTOKSIKACIJOM ALKOHOLOM: UTJECAJ ISTODOBNE INGESTIJE DRUGIH TVARI I ZBRINJAVANJA DIŠNOG PUTA – RETROSPEKTIVNA KOHORTNA STUDIJA TIJEKOM 36 MJESECI

***Matilda Kambo[1,2], Klerida Shehu[2], Jonida Kito[1,2], Benard Shehu[2], Albana Kociaj[1,2], Eneida Hoxha[2], Andrin Tahiri[1], Rudin Domi[2]**

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Abstract

Background: Severe alcohol intoxication may cause coma and respiratory failure, aggravated by co-ingested central nervous system depressants. We evaluated respiratory depression and the association of opioid or benzodiazepine co-ingestion with endotracheal intubation and outcomes.

Materials and methods: This retrospective single-centre cohort included adults admitted with toxicologically confirmed alcohol-related coma between January 2023 and December 2025. Patients were classified as having isolated alcohol intoxication, alcohol–benzodiazepine co-ingestion, or alcohol–opioid co-ingestion. Admission Glasgow Coma Scale (GCS), arterial pH, $PaCO_2$, endotracheal intubation, and in-hospital mortality were compared. Firth-penalized logistic regression was exploratory.

Results: Among 48 patients, 25 had isolated alcohol intoxication, 13 benzodiazepine co-ingestion, and 10 opioid co-ingestion. Age, sex, and blood alcohol concentration were comparable. Across these groups, mean GCS decreased (7.8, 6.5, and 5.0; $p<0.001$), arterial pH declined (7.30, 7.26, and 7.22; $p=0.003$), and $PaCO_2$ increased (48.2, 55.1, and 62.0 mmHg; $p=0.008$). Intubation rates were 48.0%, 76.9%, and 90.0%, respectively ($p=0.031$). Intubated patients had lower GCS and pH and higher $PaCO_2$ than non-intubated patients (all $p<0.001$), whereas blood alcohol concentration did not differ. Two deaths occurred, both after mixed intoxication ($p=0.178$). In severity-adjusted exploratory analysis, GCS was the strongest correlate of intubation (OR 0.08 per point; 95% CI <0.01–0.33; $p<0.001$).

Conclusion: Co-ingestion, particularly of opioids, identified patients with more severe neurological and respiratory compromise. Integrated neurological, respiratory, and toxicological assessment may guide individualized airway management better than blood alcohol concentration alone. Larger prospective multicentre studies are required.

Keywords: alcohol intoxication; airway management; benzodiazepines; coma; endotracheal intubation; opioid co-ingestion; respiratory depression.

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Sažetak

Uvod: Teška akutna intoksikacija alkoholom može uzrokovati komu i respiratorno zatajenje, dodatno pogoršane istodobnom ingestijom depresora središnjega **živčanog** sustava. Procijenili smo respiratornu depresiju i povezanost istodobne ingestije opioida ili benzodiazepina s endotrahealnom intubacijom i ishodima.

Materijali i metode: Ova retrospektivna jednocentrična kohortna studija obuhvatila je odrasle hospitalizirane od siječnja 2023. do prosinca 2025. zbog toksikološki potvrđene kome povezane s alkoholom. Bolesnici su razvrstani u skupine s izoliranom intoksikacijom alkoholom te istodobnom ingestijom benzodiazepina ili opioida. Uspoređeni su Glasgow Coma Scale (GCS), arterijski pH, $PaCO_2$, endotrahealna intubacija i bolnička smrtnost. Firthova penalizirana logistička regresija bila je eksploratorna.

Rezultati: Od 48 bolesnika, 25 je imalo izoliranu intoksikaciju alkoholom, 13 istodobnu ingestiju benzodiazepina, a 10 opioida. Dob, spol i koncentracija alkohola u krvi bili su usporedivi. GCS se između skupina smanjivao (7,8; 6,5; 5,0; p<0,001), arterijski pH padao (7,30; 7,26; 7,22; p=0,003), a $PaCO_2$ rastao (48,2; 55,1; 62,0 mmHg; p=0,008). Stope intubacije iznosile su 48,0%, 76,9% i 90,0% (p=0,031). Intubirani bolesnici imali su niži GCS i pH te viši $PaCO_2$ od neintubiranih (sve p<0,001), dok se koncentracija alkohola nije razlikovala. Zabilježena su dva smrtna ishoda, oba nakon mješovite intoksikacije (p=0,178). U eksploratornoj analizi prilagođenoj težini stanja GCS je bio najsnažnije povezan s intubacijom (OR 0,08 po bodu; 95% CI <0,01–0,33; p<0,001).

Zaključak: Istodobna ingestija, osobito opioida, izdvojila je bolesnike s težim neurološkim i respiratornim poremećajem. Integrirana neurološka, respiratorna i toksikološka procjena može bolje usmjeriti individualizirano zbrinjavanje dišnog puta od same koncentracije alkohola u krvi. Potrebne su veće prospektivne multicentrične studije.

Ključne riječi: benzodiazepini; endotrahealna intubacija; intoksikacija alkoholom; istodobna ingestija opioida; koma; respiratorna depresija; zbrinjavanje dišnog puta.

Introduction

Acute alcohol intoxication is a common toxicological emergency, and severe poisoning may cause profound neurological impairment, respiratory depression, aspiration, coma, and death (1–3). Airway assessment is particularly challenging because reduced consciousness does not invariably correspond to ventilatory failure; decisions should integrate Glasgow Coma Scale (GCS), airway reflexes, respiratory effort, arterial blood gas findings, and the anticipated clinical course (3,4,8). Co-ingestion of benzodiazepines or opioids may intensify central nervous system depression. Benzodiazepines potentiate GABA-mediated sedation, whereas opioids directly suppress brainstem respiratory drive and reduce responsiveness to hypercapnia; combined exposure with alcohol may therefore increase the risk of hypoventilation, carbon dioxide retention, respiratory acidosis, and airway intervention (5–7). Although acute alcohol intoxication has been widely studied, few reports have simultaneously evaluated neurological status, arterial blood gas abnormalities, toxicological co-exposure, and airway management according to the class of co-ingested depressant within a single cohort of patients with alcohol-related coma. The present study was designed to address this gap. The aim of this study was to evaluate respiratory depression among patients presenting with alcohol-related coma and to investigate the impact of concomitant opioid or benzodiazepine exposure on respiratory compromise and clinical outcomes.

Co-intoxication with alcohol and opioids or benzodiazepines increases the risk of respiratory depression, hypercapnia, respiratory acidosis, and the need for endotracheal intubation.

The primary objective was to assess the association between mixed intoxication and the need for endotracheal intubation. Secondary objectives included the evaluation of arterial blood gas abnormalities, particularly hypercapnia and respiratory acidosis, as well as in-hospital mortality by type of co-ingested central nervous system depressant.

Materials and methods

Study Design and Setting

This retrospective observational cohort study was conducted at the Clinical Toxicology Service of the University Hospital Center "Mother Teresa" (QSUT), Tirana, Albania. Adult patients admitted with alcohol-related coma between January 2023 and December 2025 were retrospectively identified

through hospital medical records. The study was designed to evaluate the impact of concomitant opioid or benzodiazepine exposure on respiratory depression, airway intervention, and short-term clinical outcomes in patients with severe acute alcohol intoxication.

Study Population

Medical records of consecutive adult patients (≥18 years) admitted during the study period were reviewed. Eligible patients had toxicologically confirmed acute alcohol intoxication associated with clinically significant impairment of consciousness requiring hospital admission and intensive monitoring. Alcohol-related coma was operationally defined as acute severe depression of consciousness predominantly attributable to ethanol after exclusion of alternative causes, including traumatic brain injury, stroke, hypoglycemia, sepsis, and primary neurological disease, on the basis of clinical evaluation and routine emergency investigations. A fixed GCS threshold was not required for inclusion because airway risk in poisoning depends on respiratory status, airway reflexes, aspiration risk, co-ingestion, and clinical trajectory in addition to GCS. Patients with incomplete medical records, unavailable arterial blood gas analysis, or missing toxicological data were excluded.

A total of 48 patients fulfilled the eligibility criteria and were included in the final analysis.

Exposure Classification

Patients were classified into three predefined exposure groups according to toxicological findings and clinical documentation: isolated alcohol intoxication, alcohol with concomitant benzodiazepine exposure, and alcohol with concomitant opioid exposure. Blood alcohol concentration (BAC) was measured on admission using standard hospital laboratory procedures. Identification of opioids and benzodiazepines was based on routine toxicological screening performed during emergency evaluation, together with the corresponding clinical findings.

Toxicological screening was performed on urine samples collected at hospital admission using qualitative immunoassay-based drugs-of-abuse assays on the Abbott ARCHITECT c8000 clinical chemistry platform. The screening panel included benzodiazepines and opiates. The manufacturer-defined qualitative cut-offs used by the laboratory were 300 ng/mL for opiates, expressed as morphine equivalents, and 300 ng/mL for benzodiazepines, expressed as oxazepam equivalents. Confirmatory gas chromatography–mass spectrometry or liquid chromatography–tandem mass spectrometry was not routinely available. Results were therefore interpreted as evidence of exposure rather than quantitative drug concentration. Potential cross-reactivity, false-positive or false-negative findings, and limited detection of some synthetic opioids were recognized limitations of the screening methodology.

Clinical Assessment and Data Collection

Demographic characteristics, toxicological findings, clinical variables, respiratory parameters, and in-hospital outcomes were extracted from electronic medical records. Demographic variables included age and sex. Neurological status at presentation was evaluated using the Glasgow Coma Scale (GCS), a validated instrument for assessing the level of consciousness in critically ill patients. Neurological assessment was performed immediately upon admission, before therapeutic interventions, whenever feasible.

Available records regarding pre-hospital or emergency department naloxone administration were also reviewed. Naloxone administration was documented in eight patients with opioid co-ingestion. The timing, dose, and immediate clinical response were not consistently recorded; naloxone was therefore summarized descriptively and was not included in inferential analyses.

Respiratory function was assessed by arterial blood gas analysis obtained at admission prior to definitive airway intervention whenever clinically possible. Arterial pH and partial pressure of arterial carbon dioxide ($PaCO_2$) were selected as objective markers of respiratory depression and ventilatory impairment because hypercapnia and respiratory acidosis represent the principal physiological consequences of central respiratory suppression during severe alcohol intoxication and mixed central nervous system depressant exposure.

Study Outcomes

The primary outcome of the study was the requirement for endotracheal intubation during hospitalization. Decisions regarding airway management were made by the treating emergency and intensive care physicians according to routine institutional practice, taking into consideration neurological status, airway protective reflexes, respiratory effort, arterial blood gas abnormalities, and the anticipated risk of respiratory deterioration rather than relying solely on the Glasgow Coma Scale, consistent with current evidence on airway management in intoxicated patients. Secondary outcomes included arterial blood gas abnormalities, particularly hypercapnia and respiratory acidosis, as well as in-hospital mortality. No predefined study protocol mandated intubation; consequently, this physician-dependent outcome may also reflect local practice variation and decision bias.

Statistical Analysis

Statistical analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were summarized as mean ± standard deviation. Categorical variables were summarized as frequencies and percentages. Distributional assumptions were assessed by graphical inspection and descriptive summary statistics. The distributions of admission GCS, $PaCO_2$, and arterial pH were additionally presented using boxplots, in which the horizontal line represents the median and the box represents the interquartile range.

Comparisons among the three intoxication groups were performed using one-way analysis of variance (ANOVA) for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Comparisons between intubated and non-intubated patients were performed

Table 1. Baseline demographic, neurological, and respiratory characteristics according to intoxication group.

Variable	Alcohol only (n=25)	Alcohol + benzodiazepine (n=13)	Alcohol + opioid (n=10)	P-value
Age, years	44.4 ± 12.1	46.2 ± 14.0	47.3 ± 12.5	0.813
Male sex, n (%)	18 (72.0)	9 (69.2)	9 (90.0)	0.461
Blood alcohol concentration (mg/dL)	292.1 ± 53.9	291.9 ± 54.0	291.9 ± 54.0	1.000
Glasgow Coma Scale	7.8 ± 1.3	6.5 ± 1.1	5.0 ± 1.3	<0.001
Arterial pH	7.30 ± 0.06	7.26 ± 0.07	7.22 ± 0.05	0.003
$PaCO_2$ (mmHg)	48.2 ± 9.7	55.1 ± 12.2	62.0 ± 15.0	0.008

Values are presented as mean ± SD or number (%). Comparisons were performed using one-way ANOVA for continuous variables and χ^2 or Fisher's exact test for categorical variables.

Table 2. Clinical outcomes according to intoxication group

Outcome	Alcohol only (n=25)	Alcohol + benzodiazepine (n=13)	Alcohol + opioid (n=10)	P-value
Endotracheal intubation, n (%)	12 (48.0)	10 (76.9)	9 (90.0)	0.031
In-hospital mortality, n (%)	0 (0.0)	1 (7.7)	1 (10.0)	0.178

Values are presented as number (%). Comparisons were performed using Fisher's exact test.

using Student's *t*-test for continuous variables and the chi-square or Fisher's exact test for categorical variables.

To further investigate factors associated with endotracheal intubation, sequential Firth-penalized logistic regression models were constructed. Firth penalization was selected because of the relatively small sample size, sparse subgroup structure, and the possibility of quasi-complete separation. Initial models evaluated the association between intoxication group and airway intervention, whereas subsequent models incorporated blood alcohol concentration and neurological status (GCS). Covariates were restricted to a small number of clinically selected variables. Model discrimination was assessed using receiver operating characteristic (ROC) analysis and the apparent area under the ROC curve (AUC). Given the limited sample size and absence of internal or external validation, all regression and AUC analyses were considered exploratory and hypothesis-generating rather than confirmatory measures of predictive performance.

All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 48 patients with toxicologically confirmed alcohol-related coma were included in the study. Of these, 25 patients (52.1%) had isolated alcohol intoxication, 13 (27.1%) had concomitant benzodiazepine exposure, and 10 (20.8%) had concomitant opioid exposure.

Baseline demographic characteristics were comparable across the three groups. No statistically significant differences were observed in age, sex distribution, or blood alcohol concentration, indicating similar levels of alcohol exposure at presentation (Table 1).

In contrast, significant differences were identified in neurological and respiratory parameters. Admission Glasgow Coma Scale (GCS) scores progressively decreased from patients with isolated alcohol intoxication to those with benzodiazepine and opioid co-ingestion (p<0.001). Similarly, arterial pH declined while $PaCO_2$ increased across exposure groups, demonstrating progressively more severe respiratory compromise in patients with mixed intoxication. Patients with alcohol–opioid co-ingestion exhibited the lowest GCS scores, the highest $PaCO_2$ values, and the lowest arterial pH values, indicating the greatest degree of respiratory depression at presentation (Figures 2–4).

Distribution of admission Glasgow Coma Scale (GCS) scores in patients with isolated alcohol intoxication, alcohol–benzodiazepine co-ingestion, and alcohol–opioid co-ingestion. Boxes represent the interquartile range (IQR), the horizontal line indicates the median, whiskers extend to 1.5 × IQR, and individual points represent individual patients.

Distribution of admission arterial $PaCO_2$ values among the three intoxication groups. Boxes represent the interquartile range (IQR), the horizontal line indicates the median, whiskers extend to 1.5 × IQR, and individual points represent individual patients.

Distribution of admission arterial pH values among the three intoxication groups. Boxes represent the interquartile range (IQR), the horizontal line indicates the median, whiskers extend to 1.5 × IQR, and individual points represent individual patients. The dashed horizontal line indicates the predefined threshold for severe respiratory acidosis (pH 7.25).

Table 3. Characteristics of intubated and non-intubated patients

Variable	Intubated (n=31)	Non-intubated (n=17)	P-value
Age, years	46.8 ± 12.9	43.1 ± 12.7	0.347
Male sex, n (%)	24 (77.4)	12 (70.6)	0.598
Blood alcohol concentration (mg/dL)	294.2 ± 52.1	288.1 ± 56.7	0.703
Glasgow Coma Scale	5.9 ± 1.5	8.2 ± 1.0	<0.001
Arterial pH	7.24 ± 0.06	7.31 ± 0.05	<0.001
$PaCO_2$ (mmHg)	58.8 ± 13.2	45.6 ± 8.1	<0.001

Continuous variables were compared using Student's t-test and categorical variables using χ^2 or Fisher's exact test.

Clinical Outcomes

Clinical outcomes according to intoxication group are summarized in Table 2.

Overall, 31 of 48 patients (64.6%) required endotracheal intubation during hospitalization. The frequency of airway intervention increased progressively according to the pattern of intoxication, ranging from isolated alcohol intoxication to alcohol–benzodiazepine and alcohol–opioid co-ingestion (Figure 1). Patients with opioid co-ingestion demonstrated the highest intubation rate, consistent with the greater severity of neurological impairment and ventilatory dysfunction observed at admission.

Percentage of patients requiring endotracheal intubation in the three intoxication groups: isolated alcohol intoxication (12/25, 48.0%), alcohol–benzodiazepine co-ingestion (10/13, 76.9%), and alcohol–opioid co-ingestion (9/10, 90.0%).

Overall, in-hospital mortality was low (2/48, 4.2%). Both deaths occurred in patients with mixed intoxication, whereas no deaths were recorded among patients with isolated alcohol intoxication. Although this difference did not reach statistical significance, the observed pattern suggests greater clinical severity in patients exposed to additional central nervous system depressants.

Naloxone administration was documented in eight patients, all in the alcohol–opioid co-ingestion group. Because the timing, dosage, and immediate clinical response were inconsistently documented, no inferential analysis of naloxone response was performed.

Respiratory Depression According to Intoxication Pattern

Objective markers of respiratory function demonstrated a clear gradient of increasing physiological impairment across the three exposure groups.

Admission GCS decreased progressively in parallel with worsening arterial blood gas abnormalities. Patients with concomitant opioid exposure presented with the greatest degree of hypercapnia and respiratory acidosis, whereas patients with isolated alcohol intoxication showed the least severe physiological abnormalities. Patients with alcohol–benzodiazepine co-ingestion demonstrated intermediate findings between these two groups.

The distribution of individual GCS, $PaCO_2$, and arterial pH values is illustrated in Figures 2–4. These data demonstrate a consistent association between mixed intoxication, impaired consciousness, progressive carbon dioxide retention, and worsening respiratory acidosis.

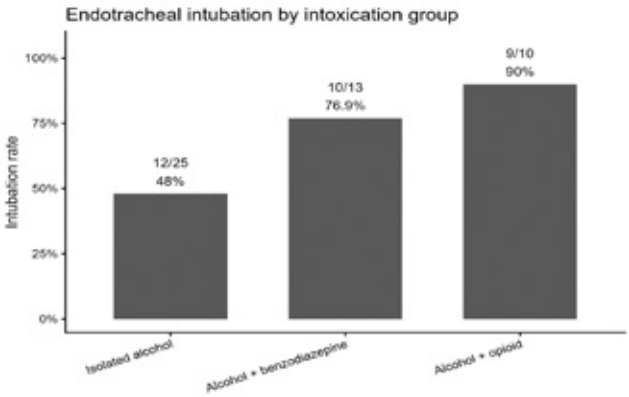

Figure 1. Endotracheal intubation rates according to intoxication group.

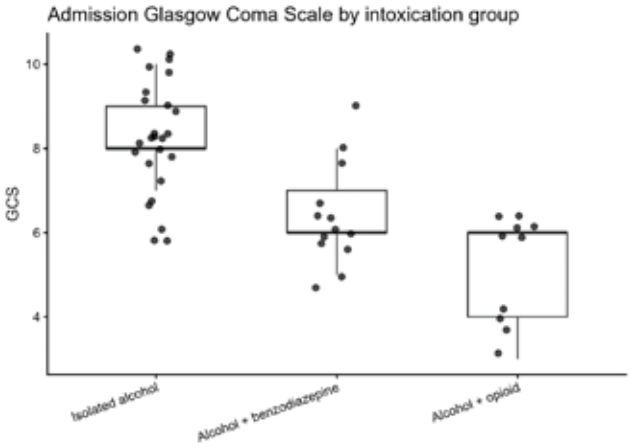

Figure 2. Admission Glasgow Coma Scale according to the intoxication group.

Factors Associated with Endotracheal Intubation

To further characterize factors associated with airway intervention, patients were stratified according to intubation status (Table 3).

Compared with non-intubated patients, those requiring endotracheal intubation presented with significantly lower admission GCS scores, lower arterial pH values, and substantially higher $PaCO_2$ concentrations. In contrast, age, sex distribution, and blood alcohol concentration did not differ significantly between the two groups.

These findings indicate that objective measures of neurological depression and ventilatory impairment were more closely associated with the need for endotracheal intubation than demographic characteristics or blood alcohol concentration alone.

Multivariable Analysis of Endotracheal Intubation

Exploratory Firth-penalized logistic regression was performed to examine factors associated with endotracheal intubation. Sequential adjustment demonstrated that neurological impairment and respiratory dysfunction provided incremental prognostic information beyond intoxication pattern and blood alcohol concentration (Table 4).

After incorporating the Glasgow Coma Scale into the model, the apparent AUC was 0.947 (95% CI 0.891–1.000). This estimate represents unvalidated within-cohort discrimination and may be inflated by overfitting because of the limited sample size.

These exploratory findings require confirmation in larger prospective cohorts with internal and external validation.

Discussion

This retrospective study suggests that concomitant central nervous system depressants, particularly opioids, identify patients with more severe neurological and respiratory compromise despite comparable blood alcohol concentrations. The principal clinical interpretation is not that intoxication pattern alone determines the need for intubation, but that suspected co-exposure should prompt integrated assessment of consciousness, ventilatory status, arterial blood gas abnormalities, airway reflexes, and the anticipated clinical course. Respiratory depression remains one of the most clinically important complications of severe acute alcohol intoxication and a major determinant of morbidity in patients presenting with impaired consciousness. Ethanol depresses central nervous system activity through multiple neurochemical mechanisms, thereby impairing airway-protective reflexes, reducing arousal, and attenuating ventilatory responsiveness (2). As intoxication progresses, these effects may lead to hypoventilation, carbon dioxide retention, and respiratory acidosis. In the present study, mixed intoxication was associated with significantly greater respiratory compromise than isolated alcohol intoxication, as reflected by higher $PaCO_2$ levels and lower arterial pH values. These observations support the concept that respiratory dysfunction is a principal mechanism linking mixed intoxication to adverse clinical outcomes. Conzelmann et al. demonstrated that reduced consciousness and increasing clinical severity were closely associated with aspiration risk in patients with severe acute alcohol intoxication, emphasizing the importance of comprehensive airway assessment (4).

Airway management should be guided by the overall clinical picture, including consciousness, ventilatory status, airway reflexes, and arterial blood gas abnormalities, rather than neurological status or blood alcohol concentration alone.

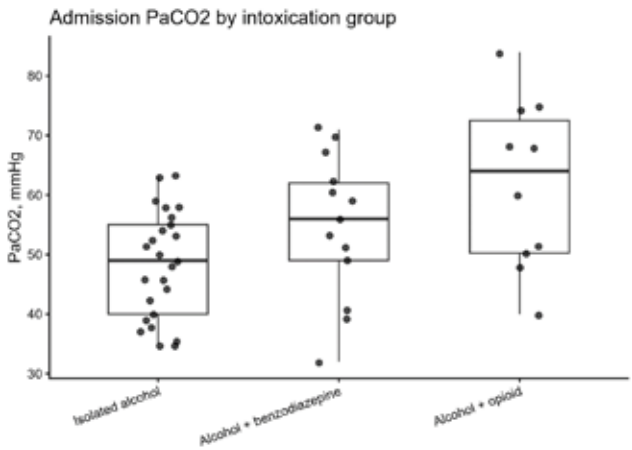

Figure 3. Admission arterial partial pressure of carbon dioxide ($PaCO_2$) according to intoxication group.

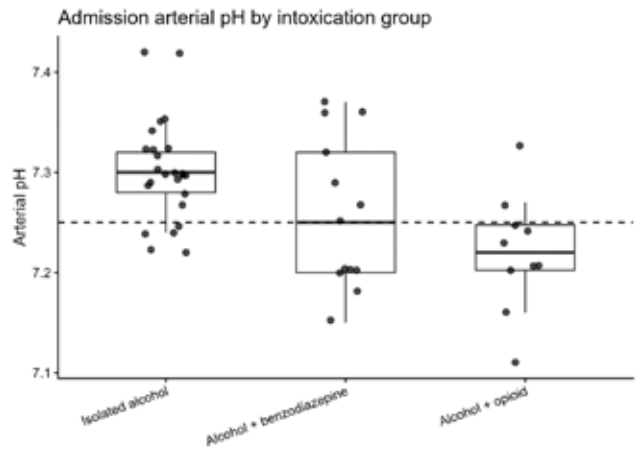

Figure 4. Admission arterial pH according to intoxication group.

Table 4. Multivariable Firth penalized logistic regression models for predictors of endotracheal intubation

Model	Variable	Adjusted OR	95% CI	P-value
Model A (Unadjusted)	Alcohol–opioid co-ingestion	4.64	0.92–46.36	0.064
Model B (BAC-adjusted)	Alcohol–opioid co-ingestion	4.59	0.92–45.61	0.064
	Blood alcohol concentration (per mg/dL)	1.00	0.99–1.01	0.934
Model C (Severity-adjusted)	Alcohol–opioid co-ingestion	0.02	<0.01–1.04	0.053
	Admission Glasgow Coma Scale (per 1-point increase)	0.08	<0.01–0.33	<0.001
	Blood alcohol concentration (per mg/dL)	1.00	0.98–1.02	0.916

**Multivariable Firth-penalized logistic regression models evaluating factors associated with endotracheal intubation. Model A examined the unadjusted association between opioid co-ingestion and endotracheal intubation. Model B additionally adjusted for blood alcohol concentration (BAC), whereas Model C further incorporated admission Glasgow Coma Scale (GCS) to assess whether the association persisted after accounting for neurological severity. Odds ratios (ORs) are presented with 95% confidence intervals (CIs). Firth-penalized logistic regression was applied to reduce small-sample bias and improve parameter estimation in the presence of sparse data. Because of the small cohort and wide confidence intervals, these models are presented as exploratory and should not be interpreted as a validated prediction model.*

Model discrimination. The apparent area under the receiver operating characteristic curve (AUC) was 0.635 for Model A and 0.947 for Model C. Although incorporation of neurological severity produced marked within-cohort separation, the high apparent AUC is likely optimistic in this small sample and may reflect model overfitting. No internal or external validation was performed; therefore, these values should not be interpreted as validated predictive performance.

Similarly, Sauter et al. reported that decisions regarding endotracheal intubation should not rely solely on neurological status but should incorporate the overall clinical presentation (3). Our findings reinforce this multidimensional approach, showing that objective indicators of ventilatory impairment closely paralleled increasing clinical severity across the exposure groups. Together, these observations suggest that arterial blood gas analysis provides clinically relevant information beyond neurological assessment alone and may facilitate early recognition of patients at increased risk of respiratory deterioration and the need for advanced airway management. This integrated approach is consistent with contemporary recommendations for the evaluation of poisoned patients, in which neurological examination, respiratory physiology, and toxicological assessment are considered complementary rather than isolated determinants of airway management decisions (12,16).

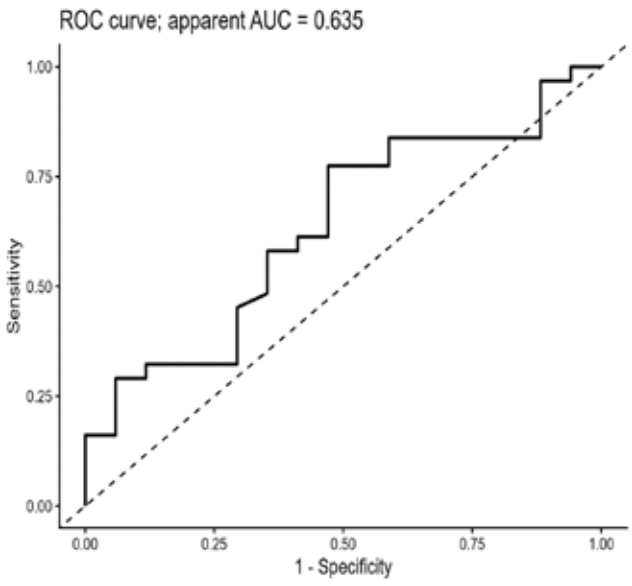

Figure 5. Receiver operating characteristic (ROC) curve of the unadjusted logistic regression model (Model A) evaluating the association between opioid co-ingestion and endotracheal intubation. The apparent area under the curve (AUC) was 0.635, indicating modest discriminative ability prior to adjustment for clinical severity.

One of the principal findings of the present study was the substantially greater respiratory compromise observed among patients with concomitant opioid exposure. Compared with both isolated alcohol intoxication and alcohol–benzodiazepine co-ingestion, patients in the opioid group exhibited the highest $PaCO_2$ values, the lowest arterial pH levels, and the greatest frequency of endotracheal intubation. Although the retrospective nature of the study precludes causal inference, these findings are biologically plausible and consistent with the established mechanisms of opioid-induced respiratory depression. Activation of μ-opioid receptors within brainstem respiratory centers suppresses respiratory drive, decreases ventilatory responsiveness to hypercapnia, and promotes progressive carbon dioxide retention (6).

When combined with alcohol, which independently depresses central nervous system function, these pharmacological effects may become synergistic, resulting in more profound impairment of consciousness and respiratory function than either agent alone (5). Our observations are consistent with previous reports demonstrating increased morbidity and mortality associated with concurrent exposure to opioids, alcohol, and other sedative agents (5,7). Tori et al. reported that alcohol and benzodiazepines were frequently involved in opioid-related overdose deaths, highlighting the clinical relevance of mixed intoxication in routine practice (7). Although mortality was uncommon in our cohort, all in-hospital deaths occurred in patients with mixed

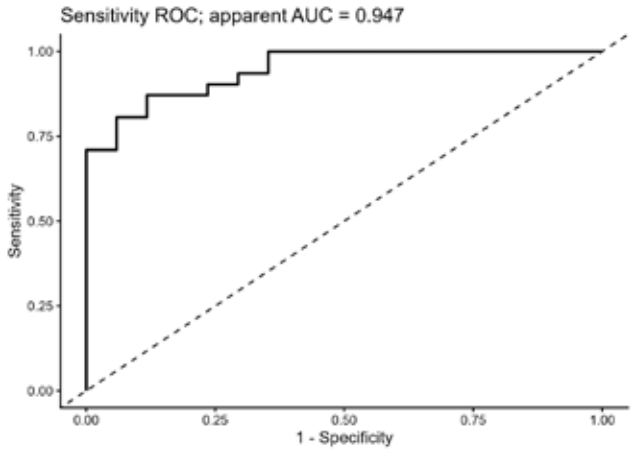

Figure 6. Receiver operating characteristic (ROC) curve of the severity-adjusted logistic regression model.

intoxication, supporting the concept that concomitant exposure to additional central nervous system depressants is associated with greater clinical severity. Moreover, the progressive decline in GCS, accompanied by increasing hypercapnia and worsening respiratory acidosis observed in the opioid group, suggests a continuum of physiological deterioration preceding the need for advanced airway intervention. These findings emphasize the importance of early recognition of opioid co-ingestion, close respiratory monitoring, and timely arterial blood gas assessment in patients presenting with alcohol-related coma, as these objective physiological markers may facilitate early identification of individuals at increased risk of respiratory decompensation and endotracheal intubation. Although the respiratory effects of benzodiazepines are generally less pronounced than those associated with opioids, their concomitant use with alcohol remains clinically important. Benzodiazepines potentiate γ-aminobutyric acid (GABA)-mediated inhibitory neurotransmission, the same neurochemical pathway through which ethanol exerts many of its sedative effects (14,15).

As a result, concurrent exposure may produce enhanced central nervous system depression, greater impairment of consciousness, and reduced protective airway reflexes compared with alcohol intoxication alone. This pharmacodynamic interaction represents a well-recognized mechanism underlying the increased clinical severity frequently observed in mixed alcohol-benzodiazepine intoxication. In the present cohort, patients with alcohol-benzodiazepine exposure demonstrated greater neurological and respiratory impairment than those presenting with isolated alcohol intoxication, although the magnitude of these abnormalities remained less pronounced than that observed among patients with opioid co-ingestion. This finding is consistent with current pharmacological understanding. While benzodiazepines may contribute substantially to sedation and impairment of airway protective mechanisms, they generally exert a less profound direct effect on ventilatory drive than opioids (5,15).

Consequently, respiratory compromise in alcohol-benzodiazepine intoxication is often mediated through a combination of reduced consciousness, impaired airway protection, and secondary hypoventilation rather than severe primary respiratory suppression. From a clinical perspective, these observations emphasize that alcohol-benzodiazepine intoxication should not be regarded as a benign condition. Even in the absence of profound hypercapnia, patients may remain vulnerable to aspiration, airway obstruction, and progressive deterioration of mental status. Previous studies have highlighted the risks associated with concurrent exposure to alcohol and benzodiazepines, particularly when additional sedative agents are present (5,7,12).

Our findings support the need for careful monitoring of this patient population and reinforce the importance of considering co-ingested substances when assessing the severity of alcohol-related coma. The management of the airway in patients presenting with alcohol-related coma remains one of the most challenging aspects of emergency and critical care practice. Although endotracheal intubation is frequently performed to protect the airway and ensure adequate ventilation, the optimal criteria for intervention remain controversial. Historically, a Glasgow Coma Scale score below 8 has often been regarded as an indication of the need for airway protection. However, accumulating evidence suggests that neurological assessment alone may not adequately identify patients at risk of respiratory deterioration (3,9,11).

Intubated patients had significantly lower arterial pH and higher $PaCO_2$, highlighting the importance of objective ventilatory abnormalities in airway decision-making.

Our findings support a more comprehensive approach to airway evaluation. Patients who underwent endotracheal intubation had significantly lower GCS scores, lower arterial pH values, and substantially higher $PaCO_2$ levels than nonintubated patients. Importantly, these observations suggest that objective evidence of ventilatory impairment contributed to clinical decision-making beyond the degree of impaired consciousness alone. Similar conclusions have been reported by Sauter et al., who observed that intubation practices in acute alcohol intoxication were influenced by the overall clinical presentation rather than GCS alone (3). Because intubation was determined by treating physicians rather

than by a study protocol, the observed associations may partly reflect local practice patterns and decision bias.

Likewise, Donald and colleagues identified several clinical factors beyond neurological status that were associated with the need for rapid sequence intubation in poisoned patients (9). Collectively, previous studies support the concept that airway management in acute poisoning should be guided by the overall clinical presentation rather than by a single neurological threshold (3,4,9,11,12). Conzelmann et al. demonstrated a close relationship between impaired consciousness and aspiration risk in severe alcohol intoxication (4), whereas Burket et al. emphasized the complexity of airway management decisions and the limitations of relying on a single clinical variable when determining the need for intubation (11). More recently, Freund et al. showed that carefully selected poisoned patients with impaired consciousness could be managed without immediate intubation under close clinical supervision, further supporting an individualized approach to airway management (12). Our findings are consistent with this evidence and suggest that airway management in alcohol-related coma should integrate neurological examination, respiratory assessment, and overall clinical status. In this context, arterial blood gas analysis appears to be a valuable adjunct, providing objective evidence of ventilatory failure and facilitating early identification of patients at increased risk of respiratory decompensation. Such a multidimensional assessment strategy is increasingly recommended in contemporary toxicology practice because no single clinical variable adequately captures the complexity of poisoning-related respiratory failure (12,16).

Early clinical assessment should integrate neurological status, respiratory physiology, and toxicological exposure to better identify patients at risk of clinical deterioration.

The multivariable analyses further reinforce the importance of objective clinical assessment. Adjustment for blood alcohol concentration did not materially alter the association between intoxication pattern and endotracheal intubation, indicating that ethanol concentration alone provides limited information regarding immediate clinical risk. In contrast, admission Glasgow Coma Scale score remained the strongest independent correlate of airway intervention, supporting the concept that clinical decision-making should be guided primarily by neurological and physiological status rather than blood alcohol concentration alone. These observations are consistent with previous reports demonstrating that the clinical manifestations of alcohol intoxication are determined not only by ethanol exposure but also by concomitant central nervous system depressants and individual physiological susceptibility. Accordingly, early assessment that integrates a neurological examination and arterial blood gas analysis may provide greater clinical value than reliance on ethanol concentration alone.

The apparent improvement in model discrimination after incorporating clinical severity variables should be interpreted with particular caution. With only 48 patients and small exposure subgroups, the AUC of 0.947 may substantially overestimate performance because of model overfitting. Formal internal validation was not feasible, and the reported discrimination therefore represents apparent rather than validated model performance. These analyses are exploratory and hypothesis-generating and require confirmation in larger prospective multicentre studies before clinical implementation.

Clinical Implications and Future Directions

The findings of the present study have several practical implications for clinicians managing patients with alcohol-related coma. First, they emphasize the importance of actively identifying concomitant opioid or benzodiazepine exposure during the initial assessment of patients presenting with impaired consciousness, as mixed intoxication was consistently associated with greater neurological and respiratory compromise. Second, the observed association between hypercapnia, respiratory acidosis, and endotracheal intubation supports the routine integration of respiratory assessment, including arterial blood gas analysis, into the evaluation of severely intoxicated patients. Finally, these findings reinforce the need for individualized airway management strategies that integrate neurological examination, respiratory physiology, and overall clinical status rather than relying exclusively on consciousness scores. Future prospective multicentre studies involving larger patient populations are warranted to externally validate these findings and further define the role of physiological markers such as $PaCO_2$ and arterial pH in predicting clinically relevant outcomes in alcohol-related coma.

Interpretation of Comparative Literature

As summarized in Table 5, the available evidence consistently supports the importance of respiratory dysfunction and individualized airway management in patients with severe alcohol intoxication and poisoning. The findings of the present study are broadly consistent with previous reports while extending current knowledge by demonstrating a clear gradient of neurological impairment, hypercapnia, respiratory acidosis, and endotracheal intubation across isolated alcohol intoxication, alcohol–benzodiazepine co-ingestion, and alcohol–opioid co-ingestion. By integrating toxicological exposure, neurological assessment, arterial blood gas analysis, and airway intervention within a single cohort, the present study provides additional evidence that objective respiratory and neurological parameters may offer greater clinical value than blood alcohol concentration alone when assessing patients with alcohol-related coma.

Limitations

This study has several limitations that should be considered when interpreting the findings. First, its retrospective single-center design introduces the possibility of selection and referral bias, as patients admitted to a tertiary intensive care

Table 5. Comparison of the Present Findings with Previous Studies

Study	Design	Population	Principal Findings	Relation to Present Findings
Sauter et al., 2020	Retrospective cohort	Acute alcohol intoxication	Intubation decisions should not rely solely on GCS.	Supports multidimensional airway assessment.
Conzelmann et al., 2021	Retrospective cohort	Severe acute alcohol intoxication	Aspiration risk increased with declining consciousness and clinical severity.	Consistent with the observed association between respiratory impairment and airway intervention.
Donald et al., 2009	Retrospective study	Poisoned patients with reduced GCS	Multiple clinical variables influenced the need for rapid sequence intubation.	Supports comprehensive clinical assessment beyond neurological status alone.
Burket et al., 2021	Narrative review	Pharmaceutical poisoning	Airway management should be individualized rather than based on a single clinical variable.	Reinforces individualized airway management strategies.
Freund et al., 2023	Randomized clinical trial	Acutely poisoned comatose patients	Selected patients may be safely managed without routine intubation under close monitoring.	Supports individualized airway management based on overall clinical assessment.
Algera et al., 2019	Review	Opioid-induced respiratory depression	Opioids suppress ventilatory drive and promote hypercapnia.	Explains the greater hypercapnia and respiratory acidosis observed in the opioid co-ingestion group.
Gudin et al., 2013	Review	Combined opioid–benzodiazepine–alcohol exposure	Combined CNS depressants markedly increase the risk of respiratory depression.	Supports the greater clinical severity associated with mixed intoxication.
Tori et al., 2020	Population-based study	Opioid overdose deaths	Alcohol and benzodiazepines frequently contribute to fatal opioid overdoses.	Consistent with the greater severity observed in mixed intoxication.
Brandenburg et al., 2017	Prediction model	Intoxicated patients	Neurological and respiratory impairment predict severe clinical outcomes.	Supports the association between respiratory compromise and endotracheal intubation.
Present study	Retrospective cohort	**48 patients with alcohol-related coma**	Mixed intoxication, particularly opioid co-ingestion, was associated with greater neurological impairment, hypercapnia, respiratory acidosis, and higher endotracheal intubation rates despite comparable blood alcohol concentrations.	Provides an integrated evaluation of toxicological exposure, neurological status, arterial blood gas abnormalities, and airway management within a single cohort of patients with alcohol-related coma.

unit may not be representative of the broader population with acute alcohol intoxication. Second, the relatively small sample size, particularly within the mixed-intoxication subgroups, limited statistical power and constrained the complexity of multivariable analyses despite the use of Firth-penalized logistic regression. Third, toxicological confirmation relied primarily on qualitative urine immunoassays, which may yield false-positive or false-negative results, are affected by cross-reactivity and sampling time, and may not detect some synthetic opioids. Fourth, endotracheal intubation was a physician-dependent outcome based on institutional practice; variability in clinical judgment and decision bias cannot be excluded. Fifth, several potentially relevant confounders, including chronic respiratory disease, chronic alcohol dependence, body mass index, aspiration events, and pre-hospital interventions, were not consistently available. The timing, dose, and immediate clinical response to naloxone were also incompletely documented. Finally, the prediction models were not internally or externally validated; the apparent AUC of 0.947 may be optimistic because of overfitting. Accordingly, the findings should be interpreted as hypothesis-generating and require external validation before routine clinical application.

Conclusions

In this retrospective cohort of patients with alcohol-related coma, concomitant opioid and benzodiazepine exposure was associated with greater neurological and respiratory impairment than isolated alcohol intoxication, with opioid co-ingestion showing the most severe physiological profile. Because of the small sample and exploratory analyses, these associations should not be interpreted as a validated prediction rule. The findings support early toxicological screening and prompt arterial blood gas analysis in patients presenting with alcohol-related coma to facilitate individualized airway

management, while confirmation in larger prospective multicentre studies is required.

Conflict of Interest

The authors declare no conflicts of interest relevant to the content of this study.

Funding

This research received no external funding.

Ethics Approval

This retrospective observational study was conducted using anonymized clinical data obtained from the Clinical Toxicology Service of the University Hospital Center "Mother Teresa" (QSUT), Tirana, Albania. The study was performed in accordance with the ethical principles of the Declaration of Helsinki and was approved by the appropriate institutional ethics committee. Due to the retrospective nature of the study and the use of anonymized patient data, the requirement for informed consent was waived.

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ORIGINAL ARTICLE / IZVORNI ZNANSTVENI ČLANAK

PREHOSPITAL DELAY IN ACUTE ISCHEMIC STROKE: RETROSPECTIVE OBSERVATIONAL COHORT STUDY

KAŠNJENJE U IZVANBOLNIČKOM ZBRINJAVANJU AKUTNOG ISHEMIJSKOG UDARA: RETROSPEKTIVNA OPSERVACIJSKA KOHORTNA STUDIJA

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Abstract

Objective: To identify factors associated with prehospital delay in patients with acute ischemic stroke and evaluate their implications for timely access to reperfusion therapies within a regional healthcare setting.

Patients and methods: This retrospective observational cohort study included 200 consecutive patients with acute ischemic stroke who presented to the Emergency Department of the University Hospital Centre Osijek during a three-month period. Early presentation was defined as arrival within 360 minutes from symptom onset. Patients with transient ischemic attack were excluded.

Results: Overall, 38.5% of patients presented within 360 minutes. In univariable analysis, early presentation was significantly associated with atrial fibrillation and a higher National Institutes of Health Stroke Scale (NIHSS) score, while wake-up stroke was strongly associated with delayed presentation. In multivariable analysis, a higher NIHSS score remained independently associated with early presentation (adjusted odds ratio [aOR] 1.11 per point increase, 95% confidence interval [CI] 1.04–1.18; P=0.001), while wake-up stroke was independently associated with delayed presentation (aOR 0.13, 95% CI 0.04–0.48; P=0.002). Early presenters were significantly more likely to receive reperfusion therapies.

Conclusion: Stroke severity is the main determinant of early hospital presentation, whereas wake-up stroke is strongly associated with delayed presentation. These findings highlight actionable targets for reducing delays. Public health strategies should emphasize recognition of mild or transient stroke symptoms and promote immediate activation of emergency medical services with the potential to improve access to reperfusion therapies and reduce the population burden of stroke.

Key words: atrial fibrillation; early diagnosis; health education; ischemic stroke

Sažetak

Cilj: Ispitati čimbenike povezane s izvanbolničkim kašnjenjem u zbrinjavanju bolesnika s ishemijskim moždanim udarom te procijeniti njihove implikacije za pravovremeni pristup reperfuzijskom liječenju u regionalnom zdravstvenom sustavu.

Ispitanici i metode: U ovo retrospektivno opservacijsko kohortno istraživanje uključeno je 200 uzastopnih bolesnika s akutnim ishemijskim moždanim udarom koji su se javili u Objedinjeni hitni bolnički prijam Kliničkog bolničkog centra Osijek u razdoblju od tri mjeseca. Rani dolazak definiran je kao dolazak unutar 360 minuta od početka simptoma. Bolesnici s tranzitornom ishemijskom atakom isključeni su iz istraživanja.

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Rezultati: Ukupno je 38,5 % bolesnika došlo unutar 360 minuta. U univarijatnoj analizi rani dolazak bio je značajno povezan s fibrilacijom atrija i višim i višim rezultatom na ljestvici moždanog udara Nacionalnog instituta za zdravlje (engl. *National Institutes of Health Stroke Scale,* NIHSS), dok je moždani udar pri buđenju (engl. *wake-up stroke*) bio povezan s kasnijim dolaskom. U multivarijatnoj analizi viši NIHSS ostao je neovisno povezan s ranim dolaskom (prilagođeni omjer izgleda [aOR] 1,11 po porastu za jedan bod, 95 % interval pouzdanosti [CI] 1,04–1,18; P=0,001), dok je moždani udar pri buđenju bio neovisno povezan s kasnijim dolaskom (aOR 0,13, 95 % CI 0,04–0,48; P=0,002). Bolesnici koji su došli ranije značajno su češće primili reperfuzijsko liječenje.

Zaključak: Težina moždanog udara glavni je čimbenik ranog dolaska u bolnicu, dok je moždani udar pri buđenju snažno povezan s kasnijim dolaskom. Ovi rezultati upućuju na potencijalne ciljeve intervencija usmjerenih na smanjenje kašnjenja. Javnozdravstvene strategije trebale bi naglasiti važnost prepoznavanja blagih ili prolaznih simptoma moždanog udara te promicati brzu aktivaciju hitnih medicinskih službi, s potencijalom poboljšanja pristupa reperfuzijskom liječenju i smanjenju populacijskog tereta moždanog udara.

Ključne riječi: fibrilacija atrija; ishemijski moždani udar; rana dijagnoza; zdravstvena edukacija

Introduction

Stroke is the leading cause of disability and the second leading cause of death in the world, with ischemic stroke accounting for the majority of the cases. According to current predictions, one in four people will have a stroke during their lifetime (1,2). It has been clearly confirmed that timely administration of reperfusion therapies – intravenous thrombolysis and mechanical thrombectomy – significantly improves the chances of a favourable functional outcome and reduces mortality compared to standard stroke treatment (3,4). Differences in their availability and strict time constraints present limitations in achieving their full potential (5). About 35% of stroke patients could potentially be treated with these advanced methods, but in practice, the number revolves around 8-10% due to untimely recognition of stroke symptoms and delayed hospital arrival (6). Prehospital delay therefore represents a major barrier to optimal stroke care and a significant public health challenge, contributing to preventable disability and increased healthcare burden.

The reasons for delayed recognition and seeking emergency medical help are multiple and include insufficient knowledge of stroke symptoms, misattribution of symptoms to benign conditions, fear or denial of the disease, as well as organizational and logistical obstacles such as geographical distance, lack of transportation or absence of witnesses to the event (7–12).

> Prehospital delay remains a major barrier to timely reperfusion therapy in acute ischemic stroke.

Although the association between stroke severity, wake-up stroke and hospital arrival time has been described previously, region-specific evidence remains important because prehospital delay is strongly influenced by local healthcare organization, EMS coverage, geography, public awareness and referral pathways. Data from Croatia and comparable regional healthcare systems are limited (13–15). Therefore, evaluating these determinants in a Croatian regional stroke-care setting may help identify whether established predictors also apply locally and whether specific system-level patterns, such as rural–urban differences or access to reperfusion therapies, require targeted intervention.

The aim of this study was to identify factors associated with prehospital delay in patients with acute ischemic stroke in a regional healthcare setting and to evaluate their implications for improving timely access to reperfusion therapies.

Materials and methods

Study design

A retrospective observational cohort study was conducted at the Emergency Department of the University Hospital Centre Osijek, a regional stroke care provider within the Croatian healthcare system. The study was approved by the Ethics Committee of the Faculty of Medicine Osijek of the Josip Juraj Strossmayer University in Osijek (Approval number: 602-04/23-08/03; 2158-61-46-23-145) and conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective design of the study and the use of anonymized clinical data.

Patients

The study included 200 consecutive patients aged ≥ 18 years and diagnosed with acute ischemic stroke who were examined at the Emergency Department of the University Hospital Centre Osijek between 1 March 2022 and 31 May 2022. Patients with transient ischemic attack were excluded.

Methods

Data were retrieved from the hospital information system, including patient´s age, sex, place of residence and pre-existing

comorbidities (hypertension, diabetes mellitus, atrial fibrillation, smoking status, coronary artery disease and previous stroke).

Patients were categorized by place of residence as either rural or urban. This classification was based on data from the Croatian Bureau of Statistics and the current administrative divisions of the Republic of Croatia (16).

Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). It was defined by NIHSS as follows: 0 – no stroke symptoms, 1 to 4 – minor stroke, 5 to 15 – moderate stroke, 16 to 20 – moderate to severe stroke and 21 to 42 – severe stroke.

The time elapsed since the first appearance of stroke symptoms, i.e., "last-seen-well", was recorded. Patients were divided into two groups: those who presented early (time elapsed ≤360 minutes) and those who presented late (>360 minutes). The 360-minute cutoff was chosen as a pragmatic threshold reflecting timely access to acute stroke evaluation and potential reperfusion pathways in a regional stroke network. However, we acknowledge that this threshold is broader than the conventional therapeutic window for intravenous thrombolysis and does not necessarily indicate optimal eligibility for all reperfusion therapies. Wake-up stroke was defined as stroke symptoms first noticed at awakening, with an unknown exact onset time. The primary outcome of interest was early hospital presentation (≤360 minutes from symptom onset), reflecting timely access to acute stroke care. Data were also collected on whether intravenous thrombolysis and/or mechanical thrombectomy were performed. A composite treatment variable, defined as receipt of any reperfusion therapy, was created to include patients who received intravenous thrombolysis, mechanical thrombectomy or both treatments. An in-hospital outcome was defined as discharge home or in-hospital death.

Statistical analysis

Categorical data were represented as absolute and relative frequencies. Numerical data were described using the median and the limits of the interquartile range. Differences in categorical variables were tested with the $\chi 2$-test. The normality of the distribution of numerical variables was tested with the Shapiro-Wilks test. Differences in numerical variables between two independent groups were tested with Mann-Whitney U test. Univariate logistic regression was used to analyse the association of individual variables with the outcome. Multivariable logistic regression analysis was subsequently conducted to identify independent factors associated with early presentation. Variables were selected a priori based on clinical relevance and potential confounding, including age, sex, NIHSS, atrial fibrillation, wake-up stroke and place of residence. Results are presented as odds ratios (ORs) for univariable analysis and adjusted odds ratios (aORs) for multivariable analysis with associated 95% confidence interval (CI). No missing data were observed for the analysed variables. All P values were two-sided. The significance level was set at Alpha = 0.05. The statistical analyses were performed with MedCalc® Statistical Software version 20.026 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022).

Results

A total of 200 patients were included in the study. The median age was 73 years (interquartile range 66-82 years). There were 97 (48.5%) patients from rural areas, while 103 (51.5%) lived in urban areas. History of atrial fibrillation was present in 53 (26.5%) patients, while stroke recurrence occurred in 51 (25.5%). With regard to the time elapsed since the onset of stroke symptoms, 77 (38.5%) patients reported within 360 minutes of the onset of symptoms, while 123 (61.5%) patients presented late. Overall, 19 patients (9.5%) received intravenous thrombolysis and 15 patients (7.5%) underwent mechanical thrombectomy. Ten patients (5.0%) received both intravenous thrombolysis and mechanical thrombectomy as bridging therapy. In total, 24 patients (12.0%) received at least one reperfusion therapy, defined as intravenous thrombolysis and/or mechanical thrombectomy. Overall, 176 patients (88%) were discharged home, whereas 24 patients (12%) died during their hospital stay (Table 1).

Table 1. Baseline demographic and clinical characteristics of stroke patients

		N (%)
Gender	Male	101 (50.5)
	Female	99 (49.5)
Place of residence	Rural	97 (48.5)
	Urban	103 (51.5)
Comorbidities	Hypertension	172 (86)
	Diabetes mellitus	66 (33)
	Atrial fibrillation	53 (26.5)
	Hyperlipidaemia	90 (45)
	Coronary artery disease	54 (27)
	Smoker	44 (25.1)
	Recurrent stroke	51 (25.5)
Wake up stroke		32 (16)
NIHSS	0	6 (3)
	1-4	86 (43)
	5-15	92 (46)
	16-20	12 (6)
	21-42	4 (2)
Last known well	≤360 minutes	77 (38.5)
	>360 minutes	123 (61.5)
Treatment	Thrombolysis	19 (9.5)
	Mechanical thrombectomy	15 (7.5)
Outcome	Discharged home	176 (88)
	Death	24 (12)
Total		200 (100)

NIHSS = National Institutes of Health Stroke Scale

Table 2. Comparison of demographic, clinical and stroke severity factors in early vs. late presenting stroke patients

Last known well		≤360 minutes N (%)	>360 minutes N (%)	P
Gender	Male	39 (38.6)	62 (61.4)	0.97
	Female	38 (38.4)	61 (61.6)	
Place of residence	Rural	38 (39.2)	59 (60.8)	0.82
	Urban	38 (36.9)	65 (63.1)	
Comorbidities	Hypertension	64 (37.2)	108 (62.8)	0.35
	Diabetes mellitus	24 (36.4)	42 (63.6)	0.66
	Atrial fibrillation	28 (52.8)	25 (47.2)	**0.01**
	Hyperlipidaemia	36 (40)	54 (60)	0.69
	Coronary artery disease	24 (44.4)	30 (56.6)	0.29
	Smoker	14 (31.8)	30 (68.2)	0.4
	Recurrent stroke	21 (41.2)	30 (58.8)	0.65
NIHSS	0	1 (16.7)	5 (83.3)	**0.006**
	1-4	24 (27.9)	62 (72.1)	
	5-15	42 (45.7)	50 (54.3)	
	16-20	9 (75)	3 (25)	
	21-42	1 (25)	3 (75)	
Wake-up stroke		3 (9.4)	29 (90.6)	**<0.001**
Treatment	Thrombolysis	18 (94.7)	1 (5.3)	**<0.001**
	Mechanical thrombectomy	15 (100)	0	**<0.001**
Outcome	Discharged home	65 (36.9)	111 (63.1)	0.22
	Death	12 (50)	12 (50)	
TOTAL		77 (38.5)	123 (61.5)	

NIHSS = National Institutes of Health Stroke Scale

There were no significant differences in early presentation according to sex (P = 0.97) or place of residence (rural vs. urban, P = 0.82). However, atrial fibrillation was significantly associated with early presentation, with 52.8% of patients with atrial fibrillation arriving within 360 minutes compared to 33.3% without (P = 0.01) (Table 2).

Patients with mild strokes (NIHSS 0-4) more frequently presented after 360 minutes, while those with more severe strokes (NIHSS 16-20) presented earlier. Notably, only 16.7% of patients with NIHSS 0 presented early, in contrast to 75% of those with NIHSS scores between 16 and 20 (P = 0.006) (Table 2). Stroke severity was significantly higher among patients presenting within 360 minutes compared to those presenting late (median [interquartile range]: 6 [3.8-14] vs. 4 [2-6], P < 0.001) (Figure 1).

Thrombolysis was significantly more frequent among patients presenting within 360 minutes compared with delayed presenters (18 vs 1 patients, P < 0.001). The single patient who received thrombolysis despite being classified in the >360-minute group had wake-up stroke. Similarly, mechanical thrombectomy was performed exclusively in early presenters (15 vs 0 patients, P < 0.001). In-hospital mortality was numerically higher among early presenters than among late presenters, but this difference was not statistically significant (15.6% vs. 9.8%, P = 0.22). This finding should be interpreted in the context of higher stroke severity among early presenters, as reflected by significantly higher NIHSS scores in this group (Table 2).

In the univariable logistic regression analysis, atrial fibrillation (OR 2.26, 95% CI 1.09–4.70, P = 0.03) and higher NIHSS score (OR 1.10 per point increase, 95% CI 1.04–1.16, P = 0.001) were significantly associated with presentation within 360 minutes from symptom onset. In contrast, wake-up stroke

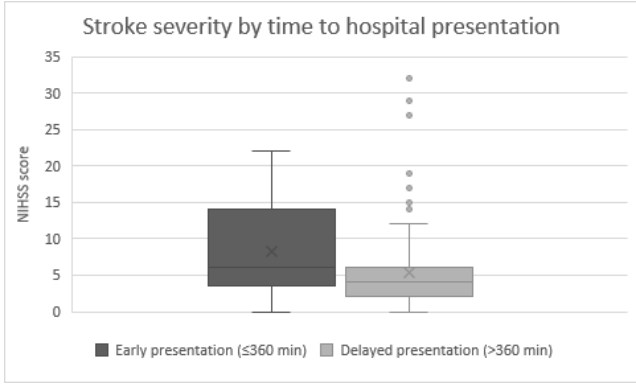

Figure 1. Stroke severity according to time to hospital presentation

Box-and-whisker plots show NIHSS scores in patients with early presentation (≤360 minutes) and delayed presentation (>360 minutes). The boxes represent the interquartile range, the horizontal line indicates the median, whiskers denote the range, and crosses represent mean values. Outliers are shown as individual points.

Table 3. Univariable logistic regression analysis of factors associated with early presentation (≤360 minutes)

Last seen well ≤360 minutes	Odds ratio	95% confidence interval	P
Age	0.98	0.95 – 1.01	0.13
Female gender	0.98	0.52 – 1.85	0.95
Rural area	1.07	0.6 – 1.89	0.82
Hypertension	0.58	0.23 – 1.41	0.23
Diabetes mellitus	0.88	0.44 – 1.74	0.71
Atrial fibrillation	2.26	1.09 – 4.7	**0.03**
Recurrent stroke	1.06	0.51 – 2.21	0.87
Coronary artery disease	1.49	0.73 – 3.02	0.27
Hyperlipidaemia	1.18	0.6 – 2.31	0.64
Wake-up stroke	0.09	0.03 – 0.29	<0.001
NIHSS (per point)	1.1	1.04 – 1.16	**0.001**
Smoker	0.73	0.35 – 1.51	0.31

NIHSS = National Institutes of Health Stroke Scale

Table 4. Multivariable logistic regression analysis of factors associated with early presentation (≤360 minutes)

Last seen well ≤360 minutes	Adjusted odds ratio	95% confidence interval	P
Age	0.97	0.94 – 1	0.08
Female gender	1.01	0.53 – 1.92	0.98
Rural area	0.88	0.47 – 1.67	0.71
Atrial fibrillation	1.96	0.95 – 4.04	0.07
Wake-up stroke	0.13	0.04 – 0.48	**0.002**
NIHSS (per point)	1.11	1.04 – 1.18	**0.001**

NIHSS = National Institutes of Health Stroke Scale

was strongly associated with delayed presentation (OR 0.09, 95% CI 0.03–0.29; P<0.001) (Table 3).

In multivariable logistic regression analysis including age, sex, NIHSS score, atrial fibrillation, wake-up stroke and place of residence, a higher NIHSS score remained independently associated with early hospital presentation (aOR 1.11 per point increase, 95% CI 1.04–1.18; P=0.001). Wake-up stroke was independently associated with a markedly lower likelihood of early presentation (aOR 0.13, 95% CI 0.04–0.48; P=0.002) (Table 4).

Discussion

In this study, early hospital presentation (≤360 minutes) was significantly associated with greater stroke severity and presence of atrial fibrillation (AF), whereas wake-up stroke was strongly associated with delayed presentation. After multivariable adjustment, higher NIHSS score and wake-up stroke remained the only independent determinants of prehospital delay.

The main findings of this study are consistent with previous evidence showing that more severe neurological deficits are associated with earlier hospital presentation, whereas wake-up stroke is associated with delayed presentation. Therefore, the primary contribution of this study is not the identification of entirely new predictors, but the confirmation and contextualization of these associations within a Croatian regional stroke-care setting, where published data remain scarce. In this cohort, only 38.5% of patients arrived within 360 minutes, while early presentation was strongly associated with access to reperfusion therapy. At the same time, no significant rural–urban difference in early presentation was observed, suggesting that, in this setting, geographical residence alone may be less important than symptom recognition and clinical presentation. These findings provide locally relevant evidence for stroke-care planning and support public health interventions focused on recognition of mild or atypical symptoms, rapid EMS activation and improved pathways for patients with wake-up stroke.

In this study, no significant differences in early presentation were observed between men and women. Recent studies indicate that the time from symptom onset to hospital arrival (onset-to-door time, ODT) in acute ischemic stroke shows modest – but consistent – differences between women and men (17,18). Factors contributing to these disparities include lower rates of emergency service use among women and a higher likelihood of living alone, both of which can delay recognition of stroke symptoms and timely medical response (19). Our findings are consistent with the evidence reported in the recent systematic review encompassing over 160,000 patients, which demonstrated that in the majority of studies, no statistically significant sex difference in pre-hospital delay for ischemic stroke was observed (20). This consistency may reflect comparable healthcare accessibility and emergency medical service (EMS) organization for men and women within the Croatian healthcare system, as well as a relatively uniform public awareness of stroke symptoms across sexes.

Recent research indicates that patients with acute ischemic stroke who live in rural areas tend to arrive at hospitals later than their urban counterparts. The study attributed much of this difference to delayed recognition of symptoms, longer ambulance-response and transport times, greater distances from stroke-ready hospitals and more frequent initial presentation to non-stroke-ready facilities in rural settings (21,22). The results of our study may be explained by the fact that all participants, regardless of whether they resided in urban or rural areas, lived relatively close to the University Hospital Centre Osijek, which is a stroke centre. This geographical proximity likely minimized differences in ODTs between groups. In addition, the Osijek EMS operates several branch stations throughout the region, which enables a timely response and facilitates rapid access to acute medical care for the local population.

In our study, conditions such as hypertension, diabetes mellitus, hyperlipidaemia, coronary artery disease and recurrent stroke did not demonstrate measurable effects on prehospital delay. This is in contrast with some previous findings suggesting that chronic disease burden may influence patients' ability to recognize symptoms or seek timely care

(23,24). On one hand, patients with chronic illness might have closer medical follow-up and higher awareness, which could favour faster recognition and hospital contact; on the other, comorbidities might impair mobility and symptom recognition or contribute to "atypical" stroke presentation, delaying decision or transport. Given the lack of consistent empirical data, such hypotheses remain speculative.

Several multicentre and registry-based analyses have observed that patients with recurrent stroke are more likely to arrive by EMS and, in some cohorts, reach the hospital sooner than those with first-ever stroke (25). Patients who survive a prior stroke often receive education about stroke signs, maintain closer contact with health services and may have written action plans or lower thresholds for calling EMS; caregivers in these households may also recognize symptoms more rapidly. On the other hand, recurrent stroke patients may have greater disability, atypical presentations or social isolation that can delay recognition and transport in some settings (26).

Our study showed an association between early presentation and AF in univariable analysis but lost statistical significance after adjustment for stroke severity. This suggests that the effect of AF is largely mediated through more severe clinical presentation rather than directly influencing patient behaviour or healthcare access. In a 2024 retrospective cohort study comparing patients with known AF and those in whom AF was first detected after stroke, there was no statistically significant difference in stroke recognition-to-door times or in rates of prehospital stroke-code activation between the groups (27). On the other hand, a 2024 Chinese multicentre study found that a history of AF was independently associated with a higher likelihood of arriving within 3 hours of symptom onset, even after controlling for distance, mode of transport and stroke severity (28). Future studies with larger sample sizes are needed to clarify the relationship between atrial fibrillation and early presentation. Nevertheless, encouraging rapid EMS activation upon symptom onset in this high-risk population could further shorten ODT and increase the proportion of patients eligible for reperfusion therapies.

Stroke severity emerged as the strongest independent determinant of early hospital presentation. Several large, contemporary studies show that greater neurological deficit at presentation is commonly associated with shorter ODT, probably because more severe deficits produce unmistakable disability that triggers rapid help-seeking and EMS activation (29,30). Conversely, patients with low NIHSS often have subtle or non-specific complaints that are commonly misattributed to benign causes or existing chronic conditions; this reduces perceived urgency and increases reliance on non-urgent care pathways, self-management or delayed presentation (31). These apparently contradictory findings suggest that the relationship between stroke severity and ODT is context-dependent and mediated by local health-seeking behaviour, transport logistics and how stroke symptoms are interpreted by laypersons and first responders. From a public health perspective, patients with less severe presentations represent a key target for intervention, as they constitute a substantial proportion of the stroke population who are less likely to present within the therapeutic time window, but still benefit from rapid assessment.

Higher stroke severity independently predicted earlier hospital presentation, whereas wake-up stroke was associated with delayed presentation

Wake-up stroke was strongly associated with delayed arrival, which is expected given the unknown symptom onset time and the use of the last-known-well concept to define onset-to-door time (32). Therefore, this finding should not be interpreted solely as a behavioural determinant of delayed help-seeking. Unlike factors such as symptom recognition, EMS activation or mode of transport, wake-up stroke is partly linked to delayed presentation by definition, because the last-known-well time usually precedes symptom discovery by several hours. In this sense, wake-up stroke represents a distinct clinical and methodological subgroup rather than a conventional modifiable determinant of prehospital delay. Its practical importance lies in the fact that conventional time-based eligibility criteria may exclude many of these patients from reperfusion therapy, despite the possibility that some may still benefit from treatment based on advanced imaging selection.

In our study, early hospital presentation was strongly associated with eligibility for advanced reperfusion therapies. Nearly one quarter of patients who presented within 360 minutes received thrombolysis and one-fifth underwent mechanical thrombectomy. On the other hand, among patients presenting beyond 360 minutes, only one patient received intravenous thrombolysis and none underwent mechanical thrombectomy. This finding highlights the important impact prehospital delay has on eligibility for time-dependent advanced stroke therapies. As mentioned above, although thrombolysis is generally limited to 4.5 hours after symptom onset, one patient in our study presented beyond 360 minutes as a wake-up stroke and received thrombolysis. However, detailed case-level imaging-selection data were not systematically captured in the retrospective dataset. Therefore, we cannot reliably determine whether thrombolysis in this case was based on CT perfusion, MRI-based mismatch assessment, or clinical reassessment by the treating stroke team. This finding should therefore be interpreted cautiously and should not be considered evidence of routine thrombolysis beyond the standard therapeutic window. Taken together, these findings emphasize that delayed presentation effectively eliminates access to reperfusion therapies for the majority of patients, representing a major barrier to optimal stroke care.

The definition of early presentation used in this study should be interpreted within the context of a pragmatic regional stroke-care pathway rather than a strict marker of optimal

eligibility for reperfusion therapies. Although a 360-minute cut-off may capture patients who still require urgent acute stroke evaluation, it is broader than the conventional therapeutic window for intravenous thrombolysis. Acute stroke treatment is increasingly guided not only by time from symptom onset but also by advanced imaging selection. In selected patients, particularly those with large-vessel occlusion or wake-up stroke, CT/MR perfusion mismatch or MRI DWI-FLAIR mismatch may support reperfusion treatment beyond conventional time-based windows. The Stroke Action Plan for Europe 2018–2030 emphasizes substantially shorter treatment-related targets, including reducing median onset-to-needle time for intravenous thrombolysis and onset-to-reperfusion time for endovascular treatment (33). Its mid-term update further stresses the importance of rapid EMS activation, shorter onset-to-door times and optimized in-hospital workflows (34). Similarly, previous studies have shown that onset-to-door time within 4.5 hours is more closely aligned with better clinical outcomes and eligibility for intravenous thrombolysis (35,36). Therefore, the proportion of early presenters in our study should not be interpreted as the proportion of patients optimally eligible for intravenous thrombolysis, but rather as the proportion reaching hospital within a broader time-sensitive acute stroke pathway.

Improved recognition of mild stroke symptoms and prompt EMS activation may reduce prehospital delay and increase access to reperfusion therapies

Beyond onset-to-door time, several system-level factors may further influence access to reperfusion therapies and clinical outcomes, including prehospital stroke recognition, hospital prenotification, door-to-needle time for intravenous thrombolysis and door-to-groin time for mechanical thrombectomy (34,37). These variables reflect the efficiency of the acute stroke pathway after first medical contact and after hospital arrival. In our setting, standardized prehospital stroke scales were not routinely used during the study period, and detailed EMS and in-hospital workflow metrics were not available for analysis. Future prospective studies should therefore incorporate prehospital recognition protocols, hospital prenotification, mode of transport, door-to-needle time and door-to-groin time to provide a more comprehensive assessment of delays across the entire stroke-care pathway.

Although early presentation is generally associated with improved access to time-dependent advanced therapies (35), there was no significant difference in in-hospital mortality in our study. This likely reflects the limited sample size and higher stroke severity among patients who presented early, which may have attenuated the potential survival benefits of earlier arrival.

Several important prehospital variables were not available, including EMS activation, mode of transport, witness presence, living status and actual distance from hospital. Their omission may have introduced residual confounding, as these factors can influence both symptom recognition and time to hospital arrival. Therefore, the associations observed for NIHSS score, wake-up stroke and rural–urban residence should be interpreted within the limitations of the available retrospective dataset.

Finally, the nationwide Helicopter Emergency Medical Service became operational in Croatia in March 2024, after the period covered by this study (38). Future studies should evaluate whether this system-level intervention reduces onset-to-door times and improves access to reperfusion therapies, particularly among patients from rural or remote areas.

These findings highlight actionable targets to reduce prehospital delay, particularly through improved public awareness of mild stroke symptoms and timely EMS activation. Addressing these factors may increase the proportion of patients eligible for reperfusion therapies and consequently improve stroke outcomes.

Limitations

This study has several limitations. First, it is a single-centre retrospective study, which may limit generalizability to other healthcare settings. Second, the time to presentation was determined using the last-known-well concept, which represents standard clinical practice and is routinely used for treatment decision-making. However, it may be subject to recall bias, which may affect the accuracy of prehospital delay estimation. Third, detailed prehospital and in-hospital workflow data were not available. Specifically, EMS activation, mode of transport, hospital prenotification, door-to-needle time and door-to-groin time were not systematically recorded and therefore could not be analysed. In addition, standardized prehospital stroke scales were not routinely used in our setting during the study period. Fourth, early presentation was defined using a 360-minute threshold, which is broader than the conventional time window for intravenous thrombolysis and may overestimate timely arrival when compared with studies using 3-hour or 4.5-hour onset-to-door thresholds. Finally, wake-up stroke is inherently linked to delayed presentation due to unknown onset time, which may influence its observed association with delayed presentation. Future prospective, multicentre studies with larger sample sizes and detailed prehospital system data are needed to better address these limitations. Future prospective, multicentre studies incorporating detailed prehospital workflow metrics are needed to validate these findings and further optimize acute stroke pathways.

Conclusion

Stroke severity is the primary independent determinant of early hospital presentation with acute ischemic stroke, while wake-up stroke is strongly associated with delayed presentation. Early presentation was strongly linked to eligibility for advanced reperfusion therapies, whereas delayed presentation almost completely eliminated access to these time-dependent therapies.

These findings highlight prehospital delay as a critical barrier to optimal stroke care and the need for targeted public health

education to improve stroke symptoms recognition – especially subtler presentations. This can increase the proportion of patients eligible for reperfusion therapies, improve functional outcomes and decrease overall stroke burden at the population level.

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REVIEW ARTICLE / PREGLEDNI ČLANAK

MANAGEMENT OF SEPSIS AND SEPTIC SHOCK IN THE EMERGENCY DEPARTMENT

ZBRINJAVANJE SEPSE I SEPTIČKOG ŠOKA U HITNOM BOLNIČKOM PRIJAMU

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Abstract

Sepsis, a rapidly progressing and life-threatening organ dysfunction, requires immediate action. Early recognition and timely intervention are critical because delays lead to high mortality. Current guidelines combine essential procedures for initial sepsis care into a one-hour bundle. This paper summarizes the most up-to-date evidence and recommendations for managing sepsis and septic shock in the emergency department. Accurate identification of sepsis and exclusion of non-infectious causes are essential. Key interventions include prompt initiation of empirical antibiotics after microbiological sampling, personalized to each patient, and initial treatment with electrolyte-balanced crystalloids guided by fluid tolerance and fluid responsiveness. Early vasopressor norepinephrine administration targets a mean arterial pressure of 65 mmHg; vasopressin may be added in refractory cases. Corticosteroids are reserved for patients with continued hemodynamic instability who do not achieve the target mean arterial pressure despite vasoactive therapy and bicarbonates for severe metabolic acidosis and acute kidney injury. Although implementing this comprehensive approach in the ED is challenging, evidence consistently shows that early, protocol-driven care improves patient outcomes.

Keywords: antibiotic; emergency medicine; sepsis; septic shock; vasopressor agents.

Sažetak

Sepsa je životno ugrožavajuća organska disfunkcija, s porastom incidencije i visokim mortalitetom. Liječenje je vremenski ovisno, te je nužno rano prepoznavanje ovih bolesnika, koji se vrlo često inicijalno zbrinjavaju u hitnom prijemu. Aktualne smjernice objedinjuju osnovne postupke početnog liječenja sepse u jednosatni snop postupaka. Cilj ovog rada je prikaz najnovijih spoznaja i rezultata studija te preporuka za osnovno liječenje sepse i septičkog šoka u hitnoj medicini. Iznimno je važno ispravno prepoznati sepsu, odnosno prepoznati neinfektivno zbivanje ako je ono uzrok stanja bolesnika. U liječenju sepse je ključna žurna primjena empirijske antibiotske terapije prilagođene osobitostima pojedinog bolesnika, odmah po uzimanju mikrobioloških uzoraka. U početno liječenje spada i volumna nadoknada, primjena elektrolitski balansiranih kristaloidnih otopina, koja je ovisna o procjeni tolerancije i osjetljivosti na primjenu tekućine, kao i rana primjena vazopresora noradrenalina s ciljem postizanja srednjeg arterijskog tlaka 65 mmHg žive, ali i izbjegavanja preopterećenja tekućinom. Ukoliko se radi o refraktornom šoku, preporučeno je uz primjenu noradrenalina dodati vazopresin. Kortikosteroidi se ne primjenjuju rutinski, ali imaju ulogu u liječenju kontinuirano hemodinamski nestabilnih bolesnika, odnosno onih u kojih se ne ostvaruje ciljna vrijednost srednjeg arterijskog tlaka usprkos vazoaktivnoj terapiji. Bikarbonati su indicirani kod bolesnika s teškom metaboličkom acidozom te akutnom ozljedom bubrega. Provođenje svih postupaka inicijalnog liječenja sepse u hitnom prijemu je osobito izazovno, ali brojne studije potvrđuju da omogućuje bolje ishode bolesnika.

Ključne riječi: antibiotici; hitna medicina; sepsa; septički šok; vazopresori

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Introduction

Early recognition, initial stabilization, and treatment of patients with sepsis in the hectic environment of the emergency department (ED) is extremely challenging. „Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection" (1). „Septic shock is defined as a subset of sepsis featuring profound circulatory, cellular, and metabolic abnormalities associated with a higher mortality risk than sepsis alone" (1). „Patients with septic shock require vasopressors to maintain a mean arterial pressure (MAP) of 65 mm Hg or higher, with a serum lactate level greater than 2 mmol/L in the absence of hypovolemia" (1). These two clinical features are associated with a hospital mortality of more than 40% (1). According to „The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis 3)", sepsis should be considered a possibility in patients with suspected infection from any source, and the use of „Quick Sequential Organ Failure Assessment (qSOFA) should be considered" (1). A score of 2 or higher indicates patients who are likely to have poor outcomes or are at increased risk of hospital mortality (1). However, the „2021 Surviving Sepsis Campaign (SSC) guidelines" do not support using qSOFA as the sole screening tool and recommend the „National Early Warning Score (NEWS), Modified Early Warning Score (MEWS), or Severe Inflammatory Response Syndrome (SIRS) score" (2). That is to say, a positive qSOFA score is a strong predictor of an unfavorable prognosis in patients with infection. It should certainly serve as a warning about the risk of sepsis, but it lacks sufficient sensitivity. There is a strong recommendation against its use as the sole tool for recognizing septic patients (2).

Early recognition of sepsis in the emergency setting is challenging, and timely prehospital assessment and treatment by emergency medical services are critical because outcomes are strongly time-dependent.

Sepsis and septic shock cases are rising worldwide, reaching 49 million yearly, and causing 11 million deaths (3). Even with better treatments, mortality remains high, about 20% or above (4, 5). Sepsis patients in emergency departments are among those with the highest mortality rates. The emergency medical service is the initial treatment site for sepsis and plays a particularly important role as the first link in the chain of care for these complex patients. Of interest are analysis data from the United States of America, which show that in 86% of patients, sepsis is diagnosed at admission. In about 80% of these patients, the ED is the place of initial management (6). Additionally, the out-of-the-hospital emergency medical services were taking care of more than 75% of the patients included in the study (7). Sepsis treatment outcomes are time-dependent, which is why protocols have been developed to help identify patients who need appropriate, strong therapy immediately. „The 2016 Surviving Sepsis Campaign" provided guidance for the management of these patients, and the 2018 update emphasized the importance of prompt treatment, presented as a „1-hour bundle" of resuscitation procedures (8). These include „measurement of serum lactate and remeasurement at 2-4 hours if ≥ 2 mmol/L, blood culture sampling before antibiotic administration, administration of broad-spectrum antibiotics, initiation of volume resuscitation of 30 ml/kg in hypotension or if lactate is ≥ 4 mmol/L, and administration of vasopressors in hypotension during or after the administration of volume replacement to maintain an MAP ≥ 65 mm Hg" (8). „The European Society for Emergency Medicine (EUSEM)" expressed concern in a position paper because of the feasibility of the „1-hour bundle", advocating evidence-based elements such as early identification of sepsis and early antibiotic administration, rather than strict time frames, and accomplishing all procedures from the bundle within an hour of triage (9). The key elements of the „1-hour bundle" are outlined in the SSC Guidelines 2021, but they ideally start within an hour of sepsis recognition and, for patients who are not in shock and are strongly suspected of infection, within three hours for starting antibiotic therapy (2). Another challenge in the acute environment of the ED is that these are often unexplained patients in whom early and quick recognition of sepsis is not easy, and some of them will have a different main diagnosis than sepsis after the completion of the assessment (10). This review will give a concise overview of sepsis and septic shock pathophysiology, accompanied by new findings and recommendations regarding the initial care of sepsis patients.

Methods

For the purposes of this review, we searched the PubMed database for literature published from 2020 to 2025. The strategy consisted of searching for given keywords from the Medical Subject Headings (MeSH) list. We further expanded the analysis by manually searching for references from the included studies.

Pathophysiology

The etiology of sepsis involves multiple factors and remains incompletely understood. Microorganisms and their toxic substances play a role in the rise of sepsis, as well as a significantly increased immune response of the organism (1,11). It also includes the activation of the complement system and the release of pro-inflammatory factors. Today's knowledge suggests that both pro-inflammatory and anti-inflammatory mediators play a role in the development of sepsis (11). However, the importance of prognostication lies in modulating large non-immune pathways (11,12). It is not entirely clear why an immune response that is normally localized can, in some cases, spread and cause sepsis. Cellular injury is a precursor to organ dysfunction.

But even with severe organ dysfunction, cell death is usually not significantly pronounced (1). Suggested processes underlying cell injury include „ischemia, apoptosis, and

cytopathic injury" (13). Recent findings emphasize the importance of patients' clinical and biological heterogeneity. Namely, their age, comorbidities, injuries, medications, and the infection site increase even more the complexity of this critical state (14,15). Sepsis can be partially presented as malignant intravascular inflammation. Malignant refers to the absence of control and self-sustainability, intravascular to the intravascular route of mediator spread through the blood, and inflammation to the features of sepsis, which are actually a markedly enhanced normal inflammatory response (16). When analyzing hemodynamic changes in these patients, septic shock is characterized by simultaneous changes in the macro- and microcirculations, ultimately resulting in an imbalance between the tissue's oxygen needs and the amount of oxygen delivered (17). One of the features of sepsis is the occurrence of absolute and relative hypovolemia, caused by pronounced arterial and venous vasodilation and increased vascular permeability.

Severe vasodilation and hypotension consequently lead to compensatory activation of the sympathetic nervous system by acting on alpha and beta adrenergic receptors. However, the effectiveness of these compensatory mechanisms is significantly lower than in other types of shock. The reasons are adrenal insufficiency, elevated levels of vasodilators such as nitric oxide (NO), and often reduced ventricular contractility in up to 60% of patients with sepsis (18). Septic cardiomyopathy is associated with endothelial and mitochondrial dysfunction, alterations in calcium metabolism, and alterations in beta-adrenergic receptors (18). It can occur immediately or during the first few days. This cardiomyopathy is reversible, but because it significantly affects compensatory mechanisms and the effectiveness of treatment, it is a key factor to consider in the care of these patients in the ED.

Sepsis causes profound microcirculatory and endothelial dysfunction, leading to impaired tissue perfusion despite changes in systemic hemodynamics.

Reducing the amount of capillaries that are fully functional is one of the key features of sepsis. It can be connected with tissue edema, external pressure on capillaries, endothelial swelling, or lumen obstruction by leukocytes and erythrocytes. Due to its role in regulating microcirculation, the endothelium is considered a crucial element in the sepsis development (19). Namely, it has a strong modulatory effect on coagulation processes and on signaling pathways for inflammatory and anti-inflammatory factors.

Endothelial cells interacting with the bacterial wall results with the changes described as „endothelial dysfunction, coagulation disorders, upregulation of adhesion molecules, and glycocalyx degradation" (13). The glycocalyx is part of the endothelium and is composed of glycoproteins and proteoglycans. Damage to its morphological and functional integrity manifests as increased vascular permeability and edema formation, elevated interstitial pressure, and, eventually, inadequate tissue perfusion (20).

Early recognition of sepsis

Sepsis is a clinical diagnosis. Anamnestic data and physical examination are particularly important, as they can reveal signs of infection and organic dysfunction. During the initial treatment of these patients, a wide range of possible differential diagnoses is often considered.

Correct diagnosis of sepsis often requires additional observation and diagnostic interventions.

Recognizing sepsis in immunosuppressed patients, the elderly, and those in the very early stages of the disease is particularly challenging. Analyses show that 20 to 40% of patients in whom sepsis is a working diagnosis during care in the ED are defined as a condition of a non-infectious nature upon completion of workup (10). Patients with these conditions, which can be called „sepsis mimics", are unlikely to benefit from all aspects of therapy aimed at treating sepsis (10). It is for these reasons that the SSC guideline has revised the timing of bundle initiation from arrival at the ED to sepsis diagnosis.

Various screening tools are helpful in the process of correctly recognizing sepsis. There are two basic forms: manual methods or the automated use of electronic health records (EHRs) (2). Commonly used clinical tools are „Systemic Inflammatory Response Syndrome (SIRS) criteria, qSOFA (Sequential Organ Failure Assessment), NEWS, and MEWS" (2). They have very different diagnostic accuracy but mostly low predictive value. So far, no validated tool has achieved reliable results.

No mortality benefit was observed with their use in the pooled analysis of three RCTs (2,21). Nevertheless, they constitute an important component of early sepsis identification, a basic prerequisite for early treatment.

A look into the near future is provided by a recent study on the child population that pointed to the possible application of the machine learning predictive model (22). It is based on the use of EHRs and can achieve positive likelihood ratios in predicting the development of sepsis over 48 hours, i.e., before the onset of organ dysfunction (22).

Initial treatment

The first step is a clinical examination and verification of the patient's vital parameters. Priority management includes airway protection (if necessary), administration of oxygen to maintain SpO2 ≥ 92%, establishment of venous access, and early application of crystalline solutions and antibiotics. Sepsis and septic shock are urgent conditions, and it is necessary to start treatment and resuscitation procedures immediately. It must not be forgotten that adherence to the applicable guidelines in their entirety is more important after sepsis is diagnosed than when it is only one of several possible reasons for the patient's condition. Therefore, a prerequisite for the

urgent initiation of therapy is the recognition of sepsis rather than other clinical diagnoses (10). Early Goal-Directed Therapy procedures, currently combined into a sepsis bundle, represent a common, standardized approach to treating sepsis. Various studies suggest that they reduce mortality, but in two meta-analyses from lower-resource countries, they were associated with increased mortality (23, 24).

Sepsis management requires immediate treatment once the diagnosis is established, while strict adherence to the full sepsis bundle may need to be adapted to the specific healthcare setting and available resources.

This points to the need for further development of guidelines tailored to different care settings and levels of care. An analysis of about 400 EDs across Europe found that only about half provided all elements of the 1-hour bundle (25). The most common deviations are due to the later recognition of these patients, which is associated with a large number of patients undergoing treatment and insufficient staff and training.

Intravenous fluids

Sepsis is characterized by severe vasoplegia that can lead to distributive shock. Early effective volume replacement is crucial in stabilizing tissue hypoperfusion caused by sepsis (2). Therefore, in clinical practice, it is important to initiate volume resuscitation immediately upon sepsis diagnosis. Knowing that these patients often have a wider list of possible causes of their condition at the beginning of treatment in the ED, if there is a high suspicion of sepsis, it is necessary to have a very low threshold for its initiation. There are two types of resuscitation fluids: crystalloid and colloid. There is a clear clinical advantage associated with crystalloid solutions compared to colloid solutions (26).

Albumin has a clear theoretical advantage in maintaining oncotic pressure. However, multiple meta-analyses and RCTs have shown that it is not associated with improved mortality (27,28). Its routine application is often limited by lower availability and higher costs, and without a clear benefit. Therefore, the „SSC guidelines 2021“ recommend considering the use of albumin in patients who have received large volumes of crystalloids (2). Colloid use, specifically hydroxyethyl starch (HES), carries significant risks in sepsis management.

HES increases the risk of acute kidney injury (AKI), which is associated with a higher mortality rate (29,30). Guideline recommendations continue to advise against its use in sepsis (2).

Crystalloid solutions, which are the fluids of choice in sepsis, are either chloride-rich [most commonly, normal saline (NS)] or balanced crystalloid solutions. For septic patients, balanced crystalloid solutions are preferred because their electrolyte composition is more similar to plasma, and because administering large amounts of saline can cause hyperchloremic acidosis. Based on available data, some studies advise using either balanced crystalloid solutions or NS for the first liter of volume compensation, but if a significant volume is required after the first liter, then balanced crystalloid solutions are recommended (31). Currently valid recommendations regarding the type of fluid for volumetric resuscitation of septic patients are actually quite uniform (2). The situation is rather different when it comes to the required total volume and the process of its application. According to the 2021 SCC guidelines, „septic patients with pronounced hypoperfusion and those in septic shock should receive at least 30 ml/kg of IV crystalloid within the first 3 hours“ (2).

In a large retrospective study that included septic patients in the ED, the group of patients who did not receive this adequate amount of volume had worse overall outcomes, regardless of comorbidities (32). However, this approach is the subject of numerous debates and, according to several studies, is questionable.

Namely, instead of aggressive volume compensation, the emphasis is increasingly on perfusion at the microcirculation level. Aggressive volume replacement may further worsen endothelial and glycocalyx dysfunction (33,34). The importance of microcirculation recovery as a key resuscitation outcome is increasingly being recognized (35). It is achieved through individualized treatment aimed at “glycocalyx resuscitation”, based on monitoring fluid tolerance and response.

Rooted in the knowledge available today, a gradual individualized method of initial volume resuscitation was proposed (36). It includes two key elements, repeated small boluses of crystalloid (250 ml to 500 ml) and continuous hemodynamic assessment (36,37). Early administration of vasopressors is necessary if there is no improvement in circulation (36). Continued fluid administration after initial resuscitation can cause volume overload, worsen acute renal injury, and increase mortality. Following a detailed initial exam, ongoing reassessment and repeated checks of the patient’s response are crucial. Around half of septic shock patients do not show increased cardiac output after a fluid bolus, or the response is short-lived. Identifying patients who respond to fluids helps guide appropriate volume therapy. It is recommended that volume resuscitation be conducted using dynamic measures (2,10).

Initial fluid resuscitation should use crystalloids, with balanced crystalloids preferred; fluid volume should be individualized according to the patient’s response, as excessive fluid administration may contribute to fluid overload and acute kidney injury.

In modern EDs, point-of-care ultrasound is a regular, significant aid in assessing the patient's condition. In this group of patients, the ultrasound role is primarily to assess volume status and fluid responsiveness. Assessment of volume status using ultrasound includes estimation of stroke volume and lung ultrasound (37). Also useful is the assessment of venous congestion by measuring intravascular distension, as indicated by a dilated inferior vena cava (IVC), or an elevated „VexUS score" (31, 37).

Interestingly, a recent RCT comparing liberal and restrictive volume administration in these patients did not show a difference in mortality at 90 days (38). Therefore, although an individualized method of application of volume resuscitation is preferred, further research is certainly necessary regarding the appropriate amount of fluids.

The management of the resuscitation process can be associated with various ways that provide insight into changes in hemodynamic status. We highlight two ways that are particularly useful and applicable in the ED. The resuscitation procedure can be guided by changes in serum lactate values as well as capillary refill time (CRT) values. In patients with elevated lactates, it is important to take into account the overall clinical situation and to consider other possible reasons for their increase. Especially from a clinical point of view, it is interesting to note that CRT is not inferior to serum lactate levels as an indicator of resuscitation efficiency (39). Consequently, CRT is recommended to guide resuscitation effects, but other perfusion methods can be used (2). The results of a recently published study, „The ANDROMEDA-SHOCK-2", suggest that the use of CRT as a clinical biomarker of tissue perfusion may reduce mortality in the early stages of septic shock (40).

Compared to usual treatment, there was no difference in mortality, but the group in which CRT and dynamic measurements were used to guide resuscitation had a 5% shorter duration of vital organ support. Furthermore, this group of patients received less fluid, and a higher proportion received vasopressor therapy.

These results further support the currently prevailing view of the key role of individualized hemodynamic resuscitation. CRT, as a practical and rapid clinical method, has a clear place in the assessment of changes in the patient's condition and the management of therapy. Given that the ED is the place of both diagnostic assessment and the beginning of treatment of septic patients, and that these patients certainly spend a certain amount of time there, hemodynamic monitoring may include some of the invasive methods, more commonly used in intensive care units, such as arterial catheters.

Finally, interestingly, the results of an RCT including more than 1,000 patients in a state of shock, half of whom had sepsis, did not show an association between arterial catheter placement and better outcomes compared with noninvasive blood-pressure monitoring (41). Mortality at 28 days was similar (34% versus 37%), and pain, bleeding, and hematomas were more common in the group with an arterial catheter (41).

Vasoactive agents

One of the key elements of the therapy of patients with sepsis is certainly vasoactive drugs. Septic shock is caused by, among other things, vasoplegia and consequent systemic vasodilation and hypotension. MAP is a key resuscitation target because it is essential for organ perfusion. Physiological mechanisms of autoregulation can preserve organ perfusion despite changes in the MAP, but when the MAP falls below a certain threshold, below 60 or 65 mmHg, autoregulation does not work, and there is a critical drop in perfusion, consequent ischemia, and organ injury. SSC guidelines 2021 define an „initial MAP target value of 65 mm Hg" (2).

In analyzing the outcomes of patients who did not achieve the target MAP, it is important to highlight the results of the permissive hypotension study (42). Namely, patients in septic shock aged 65 years and older did not show a difference in mortality between the MAP group of 60-65 mm Hg and the control group (42). Although the target value of the MAP has been defined, this is not the case when it comes to elevated values. Specifically, the upper limit of the MAP is not clearly defined. Organ injury due to vasoconstriction and microcirculatory impairment may be caused by high levels of MAP (31). However, certain groups of patients, such as those with heart failure or with increased intra-abdominal pressure, may benefit from higher MAP values (31). This was confirmed through a trial that included patients with chronic hypertension, who probably have a wider range of autoregulatory mechanisms (43). When caring for patients in septic shock, vasopressors are recommended to achieve the target MAP. According to current guidelines and recommendations, „norepinephrine is the first-line agent over other vasopressors" (2). Norepinephrine is an alpha-1 and beta-1 adrenergic agonist that primarily acts at the vascular level, causing vasoconstriction and a consequent increase in MAP (2). It also has a positive effect on myocardial contractility and cardiac output, but with very little effect on heart rate. Early norepinephrine administration may be associated with better outcomes in septic patients. One important factor is reducing the applied volume, which reduces the risk of fluid overload (44). The results of „the CENSER trial" clearly showed a correlation between more successful control of shock and early administration of norepinephrine (45).

Certainly, an important part of discussing the use of norepinephrine in the ED is the route of administration. The peripheral venous route is the preferred method of initial administration when the central venous route is unavailable or delayed (2). In patients with septic shock in whom the MAP target value has not been achieved despite norepinephrine administration, the addition of vasopressin to therapy is recommended, rather than further increasing the dose of norepinephrine

Thus, we can consider it as the second drug of choice among vasopressors that cause vasoconstriction, but by acting on other receptors, the vascular V1 receptors of smooth muscle (46). The meta-analysis showed a lower incidence of arrhythmias, especially atrial fibrillation, but no lower mortality with norepinephrine and vasopressin combined, compared to norepinephrine alone (47). The VASST study is one of the key studies in which a group comparison was conducted: one group received only norepinephrine, and the other received vasopressin added to norepinephrine (48). It showed that adding vasopressin was associated with reduced norepinephrine requirements and reduced 28-day mortality in patients with less severe septic shock (26, 48). The use of vasopressin prevents an additional increase in norepinephrine dose and reduces overall adrenergic stimulation, but its effect on mortality is unclear (31).

Early vasopressor therapy, particularly norepinephrine, may help achieve the target MAP while limiting excessive fluid administration and the risk of fluid overload.

Epinephrine is commonly considered the third-line treatment; it is suitable for patients in whom norepinephrine and vasopressin have not achieved MAP target values (2). It can be administered as an adjunct drug to norepinephrine, just like vasopressin. Its use has been associated with side effects such as tachycardia and tachypnea, but it is very useful in patients with refractory septic shock with cardiac dysfunction due to its strong beta-adrenergic effect (38).

It has a strong effect on beta-adrenergic receptors, with a positive effect on cardiac dysfunction (2). Its use is associated with side effects, including tachyarrhythmias and increased lactate levels (37).

Patients in septic shock experience pronounced hypotension, which is one of the main factors determining their mortality (46). In a crucial effort to achieve the target MAP while starting with crystalloid solutions, vasopressors are the only additional therapeutic option. Several authors agree on the justification for their use in patients who are euvolemic/hypervolemic, or in those in whom there is no increase in MAP after the administration of the initial crystalloid bolus, for example, from 5 to 10 ml per kilogram (31,46).

Recent studies strongly suggest the importance of the early initiation of vasopressors to ensure the perfusion of target organs. The proposed time frame of many authors is within an hour of diagnosis (46). This early treatment may be associated with reduced volume overload and better overall outcomes (37).

Antimicrobial therapy

Immediately after recognition of sepsis, the key role in pharmacological treatment is the urgent initiation of empirical antimicrobial therapy, after appropriate microbiological samples are obtained. Depending on the clinical evaluation, these may include blood, urine, cerebrospinal fluid, tissue samples, or other fluids. When taking blood samples for blood culture, it is important to take two vials, for aerobic and anaerobic organisms, in each set (10).

In the initial assessment of a patient with suspected sepsis, it is necessary to consider other possible causes of the patient's condition. Biomarkers such as procalcitonin (PCT) can provide very limited help in clinical evaluation and diagnosis. PCT is often used to differentiate bacterial infections from other inflammatory conditions (49). Several recent studies have suggested that, in patients with unclear clinical presentations, it can play a useful role in deciding whether to initiate antibiotics (50-52). However, it is interesting to note that PCT, along with clinical assessment, is less effective than clinical assessment alone in the decision to initiate antimicrobial therapy (2). This is also the position expressed in the SSC guidelines, as a weak recommendation (2).

Early appropriate antimicrobial therapy is crucial in sepsis, particularly in septic shock, where each hour of antibiotic delay is associated with increased mortality

When it comes to patients with suspected septic shock or those with a high suspicion of sepsis, the answer to the question of when to start antibiotic therapy is actually clear. In these two groups of patients, appropriate antibiotic therapy should be started "immediately, ideally within an hour of recognition of their condition" (2). Several studies have shown an association between the increase in mortality and the subsequent use of antibiotics, especially in septic shock (53). A retrospective analysis by Liu et al, which included 35,000 septic patients, showed that every hour of delay in antibiotic therapy is associated with an increase in mortality, which is particularly pronounced in the subgroup of patients in septic shock (54). The association is less pronounced in sepsis patients without signs of shock (54, 55).

Observational studies suggest a possible increase in mortality when the time interval exceeds 3 to 5 hours (56, 57). Therefore, SSC recommendations indicate that in this group of patients, antibiotic therapy should be initiated no later than 3 hours after the suspicion of sepsis is established (2). This period is important for carrying out the necessary diagnostic tests, confirming or excluding sepsis, and diagnosing the source. The need for early antimicrobial therapy should be weighed against the potential for unnecessary use in patients without infection.

In certain conditions, such as necrotizing infection, peritonitis, and intestinal ischemia, urgent source control is necessary. In these patients, outcomes depend on the „time to source control" (58). It's key to implement source control urgently

after diagnosis, within 6 hours, or up to 12 hours in some studies (58, 59).

Clinical and epidemiological factors guide decisions on empirical antibiotic therapy and are often complex and challenging. This is especially true in the hectic, stressful environment of the ED, where, with the inevitable dispersion of attention to a large number of critical patients and often incomplete anamnestic data, it is necessary to assess the complete clinical picture at the right time and choose the right antibiotic. The decision depends on the suspected source, anamnestic data (previous isolates and antibiotic therapy), comorbidities, and local resistance data. In septic patients initially treated in the ED, the two most common sites of infection are the respiratory tract (43%) and the urinary tract (16%) (60, 61). This should also be borne in mind when the source of infection is not clear from the clinical examination alone, and further diagnostic measures are considered.

The representation of certain microorganisms in sepsis changes over time. The microorganisms most commonly associated with sepsis are bacteria.

With the increasing number of immunosuppressed patients, the importance of fungal sepsis, particularly Candida spp.-related sepsis, is growing (10). Choosing the right antibiotic is crucial. The correct choice of antibiotic therapy is associated with better outcomes (2). However, inappropriate antibiotic selection reduces sepsis survival (62). Initial empirical antibiotic therapy depends on the source of infection and the clinical characteristics of the individual patient. In each individual case, the choice of antibiotics is conditioned by the causative agent we suspect, the presumed infection, and the condition of the specific patient. It is recommended that the broad-spectrum coverage include the most common pathogens, i.e., Gram-positive and Gram-negative bacteria (2). The most commonly isolated bacteria in septic patients whose coverage with therapy must be considered include: „Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus, Streptococcus pneumoniae“ (63).

In the selection of antibiotic therapy, the SSC guidelines provide general recommendations that should be adapted to the specific environment and clinical situation. A common initial selection of broad spectrum antibiotics includes beta lactam antibiotics (64). These are carbapenem or piperacillin-tazobactam. Third- or higher-generation cephalosporins may also be used (44). Empirical antibiotic therapy may include a single antibiotic or may be a combination of two or more antibiotics.

The multidrug therapy concept is also part of the guidelines and clinical practice.

Combination antibiotic therapy is based on the assumed higher efficiency and more reliable sensitivity of pathogens to empirical treatment. May be associated with better outcomes (65). Monotherapy, on the other hand, is associated with a lower incidence of new infections, a lower toxic effect, and lower costs. Its possible disadvantage is the lack of action on multidrug-resistant agents. A number of studies compare monotherapy and antibiotics from two different groups. Interestingly, the results of a meta-analysis did not confirm the superiority of combination versus monotherapy in patients with gram-negative agents (66,67). However, in patients with septic shock and suspected Gram-negative sepsis, combination therapy is justified, i.e., the use of two types of antibiotics that act on Gram-negative bacteria (2). For critically ill patients with multidrug-resistant pathogens (MDR), empirical treatment with two antibiotics active against Gram-negative bacteria is recommended, whereas for patients with low MDR risk, a single agent is preferred (2,68).

A particular challenge is the treatment of patients suspected of methicillin-resistant Staphylococcus aureus (MRSA). The group at high MRSA risk includes those with soft-tissue infections, line infections, hemodialysis patients, nosocomial infections, immunosuppressed individuals, and those with prior MRSA infections (31). Some studies show an increase in mortality when more than 24 hours have elapsed before administering antibiotics that cover MRSA in patients with MRSA infection (69, 70). However, an increase in mortality is also possible in those with undifferentiated sepsis, and early treatment with antibiotics covering MRSA is initiated (71).

Antibiotic selection should be individualized according to the suspected source of infection, patient characteristics, previous microbiology, and local antimicrobial resistance patterns

The guidelines therefore recommend empirical antibiotic coverage for MRSA in patients with sepsis and septic shock at high MRSA risk, but not in those at low MRSA risk (2). In the ED, vancomycin or linezolid is usually additionally used for patients with highly suspected MRSA sepsis who require dual coverage. Piperacillin-tazobactam is recommended if anaerobic coverage is required; an alternative is a combination of cefepime and metronidazole (31). For patients with septic shock and a strong suspicion of Pseudomonas infection, dual antibiotic therapy may be appropriate.

Addition of a third- or fourth-generation cephalosporin or a carbapenem should be considered to a fluoroquinolone or an aminoglycoside (8).

It is necessary to monitor and adhere to local guidelines and protocols, as they account for local antibiotic availability and patterns of resistance. When caring for patients in septic shock, it is initially necessary to administer a loading dose of broad-spectrum antibiotics. Further dosage should be adjusted based on renal and hepatic function, and the need for further therapy should be considered immediately upon receipt of culture test results.

Adjunctive therapies

Corticosteroid therapy in sepsis is still partially controversial.

Its proposed benefits in patients with septic shock include reducing adrenal insufficiency and systemic inflammation (72). However, current studies do not provide clear evidence to support their use (31, 73, 74). Studies on hydrocortisone in septic shock have shown more days without vasopressor therapy and a shorter duration of shock, but no reduction in mortality (75, 76). Based on current knowledge, corticosteroid therapy is not routinely used in patients with sepsis, but it may have benefits in selected groups of patients, such as those in refractory shock.

A recent meta-analysis demonstrated a reduction in mortality among patients treated with a combination of hydrocortisone and fludrocortisone, which warrants further investigation (77). The „SSC 2021 Guidelines" advise against routine corticosteroid use in the initial treatment of septic shock (2). They recommend intravenous corticosteroids only if the MAP target is not reached despite vasopressor therapy (2). The recommended dose of hydrocortisone is 200 mg per day, administered intravenously in 50 mg doses every 6 hours (2, 26).

Sodium bicarbonate has been considered in the treatment of septic patients because they tend to develop metabolic acidosis or lactic acidosis through various pathophysiological mechanisms.

Their use in septic patients is truly controversial, with disagreements among experts about the justification and indications for use. The studies conducted did not provide clear answers to questions about the justification for their use. Without exogenous bicarbonate, with effective therapeutic action on establishing adequate perfusion (i.e., by addressing the underlying disorder that causes shock), the expected effect is the desired correction of metabolic acidosis. The use of exogenous bicarbonate in therapy is associated with potential adverse effects, including increased carbon dioxide partial pressure, accelerated lactate formation, and increased serum sodium concentration (78). The SSC 2021 guidelines advise „against the use of bicarbonate to improve haemodynamic values for patients in septic shock and hypoperfusion induced lactic acidemia" (2).

Corticosteroids are not routinely indicated in sepsis but may be considered in refractory septic shock, while bicarbonate therapy remains reserved for selected patients with severe metabolic acidosis and acute kidney injury.

In patients with severe lactic acidosis, vasodilation, reduced left ventricular contractility, and an impaired catecholamine response result in hemodynamic instability (79). Although the use of bicarbonate is controversial, most experts agree that it is recommended in patients with metabolic acidosis, when bicarbonate levels are below 6 mEq/L, and pH is below 7.1 (79-81).

Bicarbonate therapy is not advised for patients with mild acidosis unless they also have severe acute kidney injury (82). The recent randomised controlled study did not show an association of bicarbonate administration with a reduction in mortality or organ failure in patients with severe metabolic acidosis (82). However, in a subgroup of patients with AKI, a reduction in mortality and the need for renal replacement therapy was observed.

The SSC 2021 guidelines "suggest the use of bicarbonate in patients with septic shock and severe metabolic acidosis and acute renal injury", albeit with a low level of evidence (2).

Conclusion

Sepsis is a life-threatening condition, and treatment success is time-dependent. The mortality rate of these patients is high, especially when septic shock develops. Combining the basic elements of care for septic patients into a one-hour bundle has become a common approach in the emergency department. Despite widespread acceptance, it is associated with numerous challenges. It is still questionable to what extent their full application is possible in overcrowded and overloaded EDs. It is important to note that in patients with suspected sepsis in the ED, a broader differential diagnosis should be considered, and the probability of sepsis should be assessed; therefore, diagnostic testing should be expanded early if necessary. It is crucial to balance early recognition of sepsis with early initiation of goal-directed therapy, while also recognizing and treating any other acute disorder that is causing the patient's critical condition. Early recognition of sepsis, early use of the right antibiotic, and appropriate volume resuscitation, along with early vasopressor and other supportive measures, can lead to better outcomes for patients with sepsis.

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REVIEW ARTICLE / PREGLEDNI ČLANAK

TRISMUS: A NARRATIVE REVIEW OF ETIOLOGY AND CLINICAL CHALLENGES FOR HEALTHCARE PROFESSIONALS

TRIZMUS: NARATIVNI PREGLED ETIOLOGIJE I KLINIČKIH IZAZOVA ZA ZDRAVSTVENE DJELATNIKE

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Abstract

Trismus is a clinical condition characterized by restricted mouth opening resulting from functional or structural disturbances of the masticatory system. Although often considered a symptom rather than a distinct disease, it may indicate a wide range of underlying local and systemic pathologies. This narrative review aims to provide a comprehensive overview of the etiology, clinical presentation, diagnosis, and management of trismus, with particular emphasis on its implications in emergency and critical care settings. A structured literature search was conducted using PubMed, MEDLINE, and Google Scholar, including clinical guidelines, randomized controlled trials, and observational studies relevant to difficult airway management. The etiology of trismus is multifactorial, with common causes including odontogenic infections, trauma, temporomandibular disorders, complications of dental procedures, and head and neck malignancies or their treatment. Clinically, trismus significantly affects quality of life and may lead to serious complications if not promptly recognized and managed. In emergency medicine, it represents a major challenge due to its impact on airway management, increasing the risk of difficult intubation and adverse outcomes. Current guidelines emphasize early recognition, careful planning, and the use of advanced airway techniques. A multidisciplinary approach is essential to optimize patient outcomes and minimize complications.

Key words: airway management; critical care; intubation, intratracheal; odontogenic infections; trismus.

Sažetak

Trizmus je kliničko stanje obilježeno ograničenim otvaranjem usta koje nastaje kao posljedica funkcionalnih ili strukturnih poremećaja žvačnog sustava. Iako se često smatra simptomom, a ne zasebnom bolešću, može ukazivati na širok raspon lokalnih i sistemskih patoloških stanja. Cilj ovog narativnog pregleda jest pružiti sveobuhvatan prikaz etiologije, kliničke slike, dijagnostike i liječenja trizmusa, s posebnim naglaskom na njegove implikacije u hitnoj i intenzivnoj medicini. Provedeno je strukturirano pretraživanje literature korištenjem baza PubMed, MEDLINE i Google Scholar, uključujući kliničke smjernice, randomizirana kontrolirana ispitivanja i opservacijske studije relevantne za zbrinjavanje otežanog dišnog puta. Etiologija trizmusa je multifaktorijalna, a najčešći uzroci uključuju odontogene infekcije, traumu, temporomandibularne poremećaje, komplikacije stomatoloških zahvata te maligne bolesti glave i vrata ili njihovo liječenje. Klinički, trizmus značajno utječe na kvalitetu života te može dovesti do ozbiljnih komplikacija ako se ne prepozna i ne liječi pravodobno. U hitnoj medicinskoj službi predstavlja veliki izazov zbog utjecaja na zbrinjavanje dišnog puta, povećavajući rizik od otežane intubacije i nepovoljnih ishoda. Trenutne smjernice naglašavaju važnost ranog prepoznavanja, pažljivog planiranja i primjene naprednih tehnika osiguravanja dišnog puta. Multidisciplinarni pristup ključan je za optimizaciju ishoda liječenja i smanjenje komplikacija.

Ključne riječi: intenzivna skrb; endotrahealna intubacija; odontogene infekcije; trizmus; upravljanje dišnim putem

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Introduction

Trismus is a clinical condition defined by a limited ability to open the mouth, arising from either functional disturbances or structural alterations within the masticatory system. While it is commonly regarded as a symptom rather than a distinct disease, it represents a clinically significant sign that may reflect underlying local or systemic disorders (1). This condition can substantially impair health-related quality of life (QoL), contributing to temporomandibular dysfunction (TMD), restricted food intake, muscle pain, and increased muscular tension (2).

Trismus is a multifactorial condition affecting mouth opening and function

In both dental and broader medical settings, identification of trismus is crucial, as it can compromise essential activities such as chewing, speaking, and maintaining oral hygiene. Furthermore, it presents a notable challenge in airway management, particularly during endotracheal intubation (3). In response to these risks, various professional organizations have established protocols and guidelines aimed at enhancing the safety and effectiveness of airway management (1–3).

Methodology

This manuscript is presented as a narrative review synthesizing both general information on trismus and evidence-based recommendations for managing the difficult airway. We conducted a comprehensive literature review using multiple databases, including PubMed, MEDLINE, and Google Scholar. Search terms included combinations of "difficult airway," "ICU intubation," and "trismus". Boolean operators (AND, OR) were used to expand or narrow results based on thematic relevance. We included clinical practice guidelines (e.g., American Society of Anesthesiologists [ASA] 2022 (1) and Difficult Airway Society [DAS] 2025 (3)), randomized controlled trials, observational studies, meta-analyses, and expert consensus statements relevant to adult airway management in critical care and trismus.

Etiology

The etiology of trismus is diverse and multifactorial. Odontogenic infections are among the most frequent etiologies, especially those originating in the mandibular molar region, where inflammatory processes may spread to adjacent masticatory muscles. Trauma, including mandibular fractures or soft tissue injuries, may also result in restricted mouth opening due to pain, edema, or mechanical obstruction. Furthermore, TMD are a common contributing factor, with joint dysfunction or internal derangements playing a significant role in the development of trismus.

Complication of Infection

Dental infection must be suspected in patients with acute trismus, as severe dental infections involving the masticatory muscles often cause trismus (6). Such infections have the potential to spread into adjacent fascial spaces of the head and neck, occasionally leading to serious and life-threatening complications, including cervical cellulitis and mediastinitis (7). Among dental causes, pericoronitis is particularly commonly associated with the development of trismus (8). Examples of infections from non-odontogenic sources that may trigger trismus include tonsillitis, parotid abscess, tetanus, meningitis, and brain abscess (4).

Complication of Local Anesthesia

Trismus may occur as a complication following an inferior alveolar nerve block. During the administration of this block, the masticatory muscles, mainly the medial pterygoid muscle, can be accidentally penetrated, resulting in pain-related trismus. Stretching of the affected muscle provokes pain, triggering a reflex contraction that restricts mandibular movement (4). Additionally, the formation of an intramuscular hematoma may contribute to the development of trismus. Damage to the inferior alveolar vessels can result in bleeding within the pterygomandibular space, further limiting jaw mobility (4). When trismus develops within two to three days after the procedure, it is most commonly associated with infection along the needle pathway (5).

Odontogenic infections are a leading cause of acute trismus cases

Complication of Dental Extractions

Pain, limited mouth opening, and postoperative swelling are among the most frequently observed complications following the surgical removal of mandibular third molars, which influence the patient's QoL in the postoperative period (6). These manifestations are primarily the result of the inflammatory response to surgical trauma and are short-term. The transient jaw stiffness usually peaks on the 2nd day and resolves by the end of the 1st week (7).

Sign of Temporomandibular Disorders (TMD)

Temporomandibular disorders (TMDs) encompass pain and dysfunction of the temporomandibular joint (TMJ) and the associated masticatory muscles. They are commonly present with facial and preauricular pain, joint sounds during function, and restricted mandibular movement. Consequently, patients presenting with reduced mouth opening often have an underlying TMD. Among the various subtypes, myofascial pain and disc displacement without reduction may contribute to the development of trismus (8).

Sign of Malignancy and/or complication of Head and Neck Cancer Treatment

Trismus is rarely the initial manifestation of malignancy; however, it is frequently observed in patients with head and neck cancer (9). Reported prevalence varies widely in the

literature, ranging from 0% to 100%, depending on cancer location and extent (10). Further diagnostic evaluation, including radiographic imaging and specialist referral, should be considered when trismus is accompanied by the following clinical features (11):

1. Maximal mouth opening less than 15 millimeters (mm)
2. Absence of joint clicking history
3. Pain of non-myofascial origin (e.g., neuralgia)
4. Presence of lymphadenopathy

Trismus significantly complicates airway management in emergency care

Trismus is also a frequent complication of head and neck cancer and its treatment. Recent studies report an incidence of approximately 38% to 42% among affected patients (12,13). Radiotherapy may induce fibrosis of the temporomandibular joint or masticatory muscles, resulting in restricted mouth opening. The risk of trismus is particularly increased when the medial pterygoid muscle lies within the radiation field. In addition, surgical management of head and neck malignancies may lead to scarring of the masticatory musculature, further contributing to mandibular mobility (14).

In patients who develop trismus following oncological treatment, it is essential to distinguish whether it represents a treatment-related complication or an early sign of cancer recurrence (10).

Diagnosis, clinical presentation and management

Diagnosis of trismus is primarily established through clinical evaluation, including measurement of maximal mouth opening and assessment of accompanying symptoms. A comprehensive medical and dental history is essential for identifying the underlying etiology. In cases where structural abnormalities, trauma, or neoplastic conditions are suspected, additional imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI) may be indicated (15). Clinically, trismus is characterized by a reduced interincisal distance, typically below 35 mm, whereas normal mouth opening ranges from 35 to 45 mm, with males generally exhibiting slightly greater values (approximately 40–60 mm, average 50 mm) (16).

Patients commonly report pain, stiffness, and difficulty performing everyday oral functions, including eating, speaking, and maintaining oral hygiene. In more advanced cases, nutritional intake and overall QoL may be significantly affected. The underlying cause largely determines management, with conservative treatment approaches preferred initially. These include physiotherapy with jaw-opening exercises, thermotherapy, and pharmacological interventions such as nonsteroidal anti-inflammatory drugs or muscle relaxants (9). In the presence of infection, appropriate antibiotic therapy and, when necessary, surgical drainage are required (7). Chronic or severe cases, particularly those associated with fibrosis, may necessitate more advanced treatments, including jaw mobilization devices or surgical intervention. If left untreated, trismus can result in multiple complications, such as impaired oral hygiene, increased risk of dental disease, speech difficulties, and nutritional deficiencies. Therefore, early diagnosis and appropriate management are essential to prevent long-term functional impairment (14).

Difficulties in Emergency and Clinical Care

Trismus is a well-recognized contributor to difficult airway management and represents a significant clinical challenge that requires a structured, well-prepared approach. Limitation of mouth opening directly interferes with standard airway techniques, complicating both ventilation and intubation. In severe cases, trismus can render conventional approaches, such as orotracheal intubation or the use of supraglottic airway devices, impossible. As a result, airway management in these patients remains one of the most demanding aspects of emergency and intensive care practice, where rapid decision-making and technical expertise are critical to preventing adverse outcomes.

Early diagnosis and imaging are key in identifying underlying etiology

Over the past decade, several professional associations have developed comprehensive guidelines to improve the safety and success of difficult airway management. The American Society of Anesthesiologists updated its difficult airway guidelines in 2022, emphasizing early recognition of airway difficulty, pre-procedural planning, and the integration of modern tools such as video laryngoscopy (1). Similarly, the Difficult Airway Society (DAS) published its 2025 guidelines (3), which provide a clear, stepwise algorithm for managing unanticipated difficult intubation in adults, progressing from initial intubation attempts to emergency front-of-neck access if required. In the intensive care setting, the Intensive Care Society, in collaboration with DAS, issued guidelines in 2018 that address the unique challenges of critically ill patients, particularly highlighting the importance of achieving first-pass success and minimizing hypoxia (17). Comparable recommendations have also been published by the French Society of Anesthesia and Intensive Care, as well as broader critical care organizations such as the American College of Chest Physicians and the American Thoracic Society, all reinforcing the need for preparedness and standardized approaches (18). Despite these advances, unanticipated difficult airways continue to occur and are associated with serious complications, including hypoxia, brain injury, and death. Trismus significantly contributes to this risk by impairing bag-mask ventilation and limiting access to the oropharynx. In situations where nasal intubation is contraindicated and mouth opening is severely restricted, alternative strategies such as submental intubation or awake tracheostomy may be

required. However, these techniques are invasive and carry a higher risk of complications, including infection, bleeding, fistula formation, tracheal injury, voice changes, and cosmetic deformities, when compared with standard oral intubation. For this reason, emphasis is increasingly placed on early identification of potential airway difficulty, careful planning, and the use of less invasive techniques whenever feasible (19). Predicting difficult airway scenarios remains inherently challenging. Therefore, clinicians must maintain a high level of vigilance and be prepared for unexpected difficulties in all settings. When uncertainty exists, cautious direct laryngoscopy under topical anesthesia or minimal sedation may be performed to assess the feasibility of intubation. Awake tracheal intubation, in particular, has been shown to have a high success rate and favorable safety profile, yet it remains underutilized despite being strongly recommended in cases of anticipated difficult airway (2,20).

Multidisciplinary approach improves outcomes in trismus management

Among the various etiological factors, odontogenic infections are one of the most common causes of trismus. These infections can rapidly spread to adjacent fascial spaces, increasing the risk of airway compromise and systemic complications. Prompt and effective management is therefore essential. The cornerstone of treatment is incision and drainage of the abscess, which relieves pressure, reduces swelling, and eliminates the primary source of infection, often resulting in immediate clinical improvement. Adjunctive antibiotic therapy is indicated in cases of systemic involvement, such as fever, diffuse swelling, or immunocompromised status (21,22).

In selected clinical scenarios, alternative airway techniques may provide additional options. One such method is retromolar intubation (Figure 1), which utilizes the anatomical space located posterior to the last molar, bounded by the mandibular ramus and maxillary tuberosity. This space is present in all individuals and can be accessed by retracting the angle of the mouth. Although often described as a distinct technique, many reports refer to standard intubation followed by repositioning of the endotracheal tube into the retromolar space. This approach preserves dental occlusion and offers particular advantages in maxillofacial, orthognathic, oncologic, and trauma surgeries, where surgical access and occlusal alignment are critical (23,24).

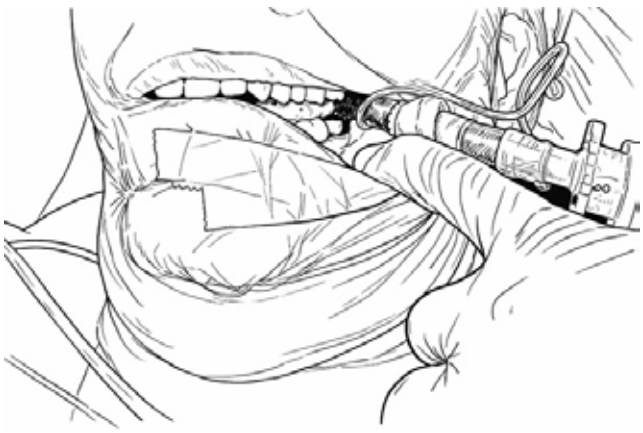

Figure 1. Retromolar intubation

Overall, the management of trismus-related difficult airway requires a multidisciplinary approach involving anesthesiologists, surgeons, and nursing staff. Continuous education, simulation-based training, and familiarity with evolving airway technologies are essential components of improving patient outcomes. Given the potentially life-threatening consequences of airway compromise, a proactive, well-coordinated strategy remains the cornerstone of safe and effective management.

Conclusion

Trismus is a multifactorial clinical condition with significant implications for both dental and medical practice. Its diverse etiology requires thorough clinical evaluation to identify the underlying cause and guide appropriate management. Beyond its impact on oral function and quality of life, trismus represents a critical concern in emergency and intensive care settings due to its association with difficult airway management. Despite advances in airway guidelines and techniques, it continues to pose a substantial challenge, particularly in unanticipated scenarios. Early recognition, accurate diagnosis, and timely intervention are essential to prevent complications and improve patient outcomes. A multidisciplinary approach, supported by adherence to evidence-based guidelines and ongoing clinician training, remains fundamental in ensuring safe and effective management of patients with trismus.

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CASE REPORT / PRIKAZ SLUČAJA

FROM PHARYNGITIS TO MULTIPLE ORGAN DYSFUNCTION SYNDROME: RAPID PROGRESSION OF INVASIVE STREPTOCOCCUS PYOGENES INFECTION

OD FARINGITISA DO VIŠEORGANSKOG ZATAJENJA ORGANA: BRZA PROGRESIJA INVAZIVNE INFEKCIJE UZROKOVANE BETA-HEMOLITIČKIM STREPTOKOKOM GRUPE A

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Abstract

Background: Invasive infections caused by *Streptococcus pyogenes* may rapidly progress from apparently uncomplicated upper respiratory tract infections to severe systemic disease with organ dysfunction.

Case presentation: A previously healthy 28-year-old male with a reported penicillin allergy presented with a four-day history of fever, sore throat, vomiting, and pleuritic chest pain. Laboratory findings demonstrated a pronounced systemic inflammatory response characterized by markedly elevated inflammatory markers, elevated lactate levels, acute kidney injury, and coagulation abnormalities. Blood cultures grew *Streptococcus pyogenes*. Imaging studies revealed a left-sided pleural effusion and a small pericardial effusion. The patient was treated with intravenous antimicrobial therapy and partial pleural drainage, resulting in clinical recovery.

Discussion: This case highlights the potential for rapid progression of invasive *Streptococcus pyogenes* infection from pharyngitis to sepsis with MODS in a young, otherwise healthy patient.

Conclusion: Early recognition and prompt treatment of invasive infections caused by *Streptococcus pyogenes* are essential for favorable outcomes.

Keywords: emergency medicine; invasive infection; multiple organ dysfunction syndrome; sepsis; streptococcus pyogenes

Sažetak

Uvod: Invazivne infekcije uzrokovane bakterijom *Streptococcus pyogenes* mogu brzo progredirati od naizgled nekompliciranih infekcija gornjih dišnih puteva do teške sistemske bolesti praćene multiorganskom disfunkcijom.

Prikaz slučaja: Prethodno zdrav 28-godišnji muškarac s alergijom na penicilin javio se zbog četverodnevnog febrilnog stanja praćenog grloboljom, povraćanjem i pleuritičkom boli u prsima. Rezultati laboratorijskih nalaza ukazali su na izrazito povišene upalne pokazatelje, laktate, akutno bubrežno oštećenje i poremećaj koagulacije. Mikrobiološkom obradom hemokultura izoliran je *Streptococcus pyogenes*. Radiološkom obradom utvrđen je lijevostrani pleuralni izljev i manji perikardni izljev. Primijenjeno je intravensko antimikrobno liječenje uz parcijalnu drenažu pleuralnog izljeva, nakon čega je uslijedio klinički oporavak.

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Rasprava: Ovaj slučaj ukazuje na mogućnost brze progresije invazivne infekcije uzrokovane bakterijom *Streptococcus pyogenes* od faringitisa do sepse sa sindromom multiorganske disfunkcije kod mladog, prethodno zdravog bolesnika.

Zaključak: Rano prepoznavanje i pravodobno liječenje invazivnih infekcija *beta-hemolitičkim streptokokom grupe A* ključni su za povoljan ishod.

Ključne riječi: hitna medicina; invazivna infekcija; sepsa; sindrom multiorganske disfunkcije; streptococcus pyogenes.

Introduction

Group *A beta-hemolytic streptococcus* (*Streptococcus pyogenes*) is a Gram-positive bacterium most commonly associated with upper respiratory tract infections, particularly pharyngitis, as well as skin and soft tissue infections. Although most infections are mild and self-limiting, invasive group A streptococcal (iGAS) infections remain an important cause of morbidity and mortality worldwide (1,2).

Clinical manifestations of invasive group A streptococcal infection include bacteremia, pneumonia, pleural infections, necrotizing fasciitis, streptococcal toxic shock syndrome (STSS), and multiple organ dysfunction syndrome (MODS) (2,3). Severe disease is associated with several virulence factors, including the M protein and streptococcal pyrogenic exotoxins, which act as superantigens and may trigger an exaggerated systemic inflammatory response, endothelial injury, coagulopathy, and multiple organ dysfunction (3). In recent years, an increase in the incidence of invasive group A streptococcal infections has been reported across several European countries and other developed regions, further emphasizing the importance of early recognition and timely treatment (4,5). Invasive infections may occur in individuals of all ages and with variable risk factors (3).

We report a case of rapidly progressive invasive *Streptococcus pyogenes* infection complicated by pleural empyema, pericardial effusion, sepsis, and multiple organ dysfunction syndrome in a previously healthy young adult.

Invasive *Streptococcus pyogenes* infection may rapidly progress from uncomplicated pharyngitis to sepsis with multiple organ dysfunction syndrome, even in previously healthy adults.

Case report

A previously healthy 28-year-old man with a history of penicillin allergy and active smoking presented to the Emergency Department with a four-day history of fever, sore throat, and vomiting. He had been treated with oral azithromycin in the outpatient setting for presumed streptococcal pharyngitis. One day before admission, he developed pleuritic pain in the left hemithorax radiating to the left shoulder.

On presentation, the patient was fully alert and afebrile (36.5 °C), but markedly tachypneic (respiratory rate 51 breaths/min) and tachycardic (heart rate 130 beats/min), with a blood pressure of 135/75 mmHg and peripheral oxygen saturation of 96% on room air. Physical examination revealed enlarged tonsils without visible exudate. Pulmonary auscultation demonstrated markedly diminished breath sounds over the left lower lung field.

Table 1. Changes in laboratory parameters during hospitalization

Parameter	On admission	During hospitalization	At discharge	Reference range
White blood cell count ($\times 10^9$/L)	11.2	24.4	7.4	3.4–9.7
C-reactive protein (mg/L)	485.4	485.4	66.8	0.2–5.0
Procalcitonin (ng/mL)	38.36	38.36	0.05	<0.10
Platelet count ($\times 10^9$/L)	76	33	432	158–424
Creatinine (µmol/L)	225	225	58	64–104
Urea (mmol/L)	12.2	20.1	<1.8	2.8–8.3
Lactate (mmol/L)	2.9	2.9	1.8	0.5–2.2
D-dimer (µg/L)	>4400	>4400	>4400	<500
Aspartate aminotransferase (AST) (IU/L)	49	49	23	11–34
Alanine aminotransferase (ALT) (IU/L)	114	114	50	9–59
Prothrombin activity (%)	73	115	102	>70
International normalized ratio (INR)	1.16	1.16	0.99	*
Fibrinogen (g/L)	5.8	>8.8	>8.8	1.8–3.5

Laboratory investigations revealed a pronounced systemic inflammatory response characterized by markedly elevated inflammatory markers and lactate levels, thrombocytopenia, acute kidney injury, and coagulation abnormalities. During hospitalization, thrombocytopenia and leukocytosis transiently worsened before inflammatory markers, renal function, and liver enzyme levels gradually normalized. The temporal changes in the main laboratory parameters are presented in Table 1.

Radiological evaluation revealed a left-sided pleural effusion with compressive atelectasis of the adjacent lung parenchyma and findings consistent with pleural empyema, together with a small pericardial effusion without hemodynamic compromise. The chest radiograph obtained on admission is shown in **Figure 1**.

Blood cultures yielded *Streptococcus pyogenes*. According to the antimicrobial susceptibility testing, the isolate was susceptible to the empirically initiated antimicrobial therapy, which was therefore continued. Based on the clinical presentation and laboratory and imaging findings, the patient was admitted to the intensive care unit with a diagnosis of sepsis complicated by pleural empyema (pleural fluid was obtained for biochemical and microbiological analysis), pericarditis, acute kidney injury, and sepsis-induced coagulopathy. The NEWS2 score on admission was 5, indicating an intermediate risk of clinical deterioration. Empirical intravenous antimicrobial therapy with meropenem and clindamycin was initiated together with supportive treatment and low-molecular-weight heparin. Partial drainage of the pleural space was performed. Because of the markedly elevated D-dimer levels, pleuritic chest pain, and tachypnea, pulmonary embolism was initially considered in the differential diagnosis but was excluded by computed tomography pulmonary angiography. Deep vein thrombosis was excluded by duplex ultrasonography of the lower-extremity veins.

During hospitalization, inflammatory markers gradually declined, renal function recovered, and the platelet count normalized. After 24 days of hospitalization, the patient was discharged home afebrile, without respiratory symptoms, and in good clinical condition. At discharge, elevated D-dimer levels persisted, consistent with the recent septic state.

Discussion

This case illustrates the rapid progression from acute pharyngitis to sepsis with multiple organ dysfunction in a previously healthy young adult. The patient fulfilled the *Sepsis-3* criteria for sepsis, presenting with acute kidney injury and coagulation abnormalities. These findings represent organ dysfunction secondary to sepsis and reflect the well-established pathophysiological mechanisms of invasive group A streptococcal infection, including systemic inflammatory response and activation of the coagulation cascade (2,5).

A particularly noteworthy feature of this case was the simultaneous involvement of the pleura and pericardium. Pleural empyema is a rare but well-recognized complication of invasive group A streptococcal infection, whereas pericardial involvement is considerably less common and has mainly been described in isolated case reports (6,7). In our patient, imaging studies demonstrated pleural empyema, while echocardiography revealed a small circumferential pericardial effusion without hemodynamic significance.

Early recognition, prompt antimicrobial therapy, and timely source control are essential for favorable clinical outcomes.

Management of invasive group A streptococcal infection is based on early administration of appropriate antimicrobial therapy and prompt source control. In addition to beta-lactam antibiotics, clindamycin plays an important role because of its ability to inhibit streptococcal toxin production and is therefore recommended in severe invasive disease (2). In the present case, early recognition of sepsis, prompt initiation of antimicrobial therapy, and partial drainage of the pleural empyema resulted in complete clinical recovery.

Conclusion

This case demonstrates that invasive group A streptococcal infection may rapidly progress from apparently uncomplicated pharyngitis to sepsis with multiple organ dysfunction syndrome, even in previously healthy individuals. Early recognition of invasive disease, timely diagnostic evaluation, and prompt initiation of appropriate treatment are essential for achieving a favorable clinical outcome.

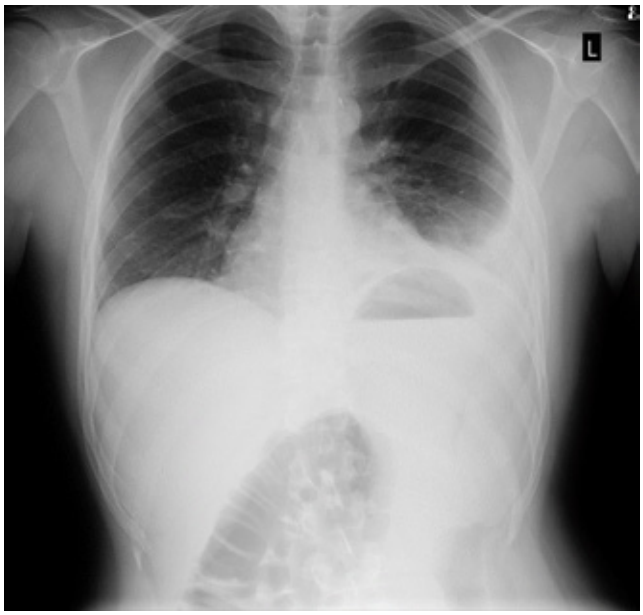

Figure 1. Chest radiograph on admission

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CASE REPORT / PRIKAZ SLUČAJA

RHABDOMYOLYSIS AS A RESULT OF CAFFEINE INTOXICATION IN A SUICIDE ATTEMPT: A CASE REPORT

RABDOMIOLIZA KAO POSLJEDICA INTOKSIKACIJE KOFEINOM U POKUŠAJU SUICIDA: PRIKAZ SLUČAJA

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Abstract

Background: Caffeine intoxication is an increasingly recognized clinical entity due to the widespread availability of caffeine-containing products. Among its broad spectrum of cardiovascular and metabolic manifestations, severe complications such as rhabdomyolysis may also occur.

Case presentation: A 19-year-old male patient was admitted to the emergency department due to intoxication. As reported by the out-of-hospital emergency care physician, the patient ingested 200 tablets, each containing 200 mg of caffeine. Symptoms included sinus tachycardia with a heart rate of 140/min without hemodynamic compromise, profuse vomiting of dark-colored content, and agitation. Initial laboratory tests demonstrated leukocytosis, hypokalemia and mixed acid-base disturbance. The patient was initially treated with symptomatic and supportive therapy. An increasing trend of creatine kinase (500 IU/L to >5000 IU/L) suggested rhabdomyolysis. Therefore, he was admitted to the intensive care unit. Improvement in somatic condition and hemodynamic stabilization were observed. The patient was discharged and referred for further treatment at a psychiatric institution.

Discussion: This case illustrates the variability in the clinical presentation of caffeine intoxication, with rhabdomyolysis but without malignant arrhythmias or acute kidney injury despite ingestion of a potentially lethal dose.

Conclusion: Early supportive therapy, close clinical observation and awareness of less common manifestations are essential for achieving favorable outcomes in patients with caffeine intoxication.

Keywords: caffeine; rhabdomyolysis; tachycardia; toxicology

Sažetak

Uvod: Intoksikacija kofeinom sve se češće pojavljuje kao klinički entitet zbog široke dostupnosti proizvoda koji sadrže kofein. Uz širok spektar kardiovaskularnih i metaboličkih manifestacija mogu se javiti i teške komplikacije, poput rabdomiolize.

Prikaz slučaja: Devetnaestogodišnji muškarac zaprimljen je u hitni bolnički prijam zbog intoksikacije. Prema navodu liječnika izvanbolničke hitne medicinske službe, bolesnik je konzumirao 200 tableta, od kojih je svaka sadržavala 200 mg kofeina. Simptomi su bili sinusna tahikardija frekvencije 140/min bez hemodinamske nestabilnosti, obilno povraćanje tamnog sadržaja i psihomotorni nemir. Početni laboratorijski nalazi pokazali su leukocitozu, hipokalemiju i miješani acidobazni poremećaj. Primijenjeno je simptomatsko i suportivno liječenje. Porast vrijednosti kreatin-kinaze (od 500 IU/L do >5000 IU/L) upućivao je na razvoj rabdomiolize, zbog čega je bolesnik premješten u jedinicu intenzivne medicine. Tijekom hospitalizacije došlo je do poboljšanja somatskog stanja i hemodinamske stabilizacije. Bolesnik je otpušten iz bolnice te upućen na daljnje psihijatrijsko liječenje.

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Rasprava: Ovaj prikaz slučaja pokazuje veliku varijabilnost kliničke slike intoksikacije kofeinom, pri čemu se unatoč unosu potencijalno letalne doze razvila rabdomioliza, ali bez malignih aritmija i akutnog bubrežnog oštećenja.

Zaključak: Rano suportivno liječenje, pomno kliničko praćenje i prepoznavanje rjeđih manifestacija ključni su za postizanje povoljnog ishoda u bolesnika s intoksikacijom kofeinom.

Ključne riječi: kofein; rabdomioliza; tahikardija; toksikologija

Introduction

Caffeine is currently regarded as the most widely used psychostimulant in the world and is available in many foods, beverages and nutritional supplements (1,2). Although generally considered safe at moderate doses, below 400 mg per day, caffeine intake can cause toxicity at much higher, gram quantities (2). Caffeine is absorbed from the gastrointestinal tract within 45 minutes, reaching almost complete bioavailability (1). High caffeine doses induce sympathetic nervous system activity through adenosine antagonism and phosphodiesterase inhibition, resulting in positive chronotropic and inotropic effects. By elevating the intracellular cyclic adenosine monophosphate and calcium levels, cardiac contractility is additionally enhanced. This mechanism may contribute to the development of arrhythmias (3). The clinical presentation of acute caffeine intoxication includes cardiovascular, metabolic, gastrointestinal, neurological/psychological, musculoskeletal and pulmonary symptoms. Although rare, renal failure has also been described secondary to rhabdomyolysis. The cause of this rare clinical feature lies in the induced intracellular calcium release which increases contractile force in the skeletal muscles (2,3). The clinical symptoms are dose-dependent, from mild stimulation to intoxication, which can occur at about 1-2 g of caffeine or serum concentration of >15 mg/L (1). The pharmacokinetic properties of caffeine, such as low plasma protein binding and low volume of distribution, make hemodialysis an effective treatment option in severe intoxication (2).

Caffeine intoxication may cause rhabdomyolysis and acute kidney injury.

Case presentation

A 19-year-old male patient was admitted to the emergency department due to intoxication. As reported by the out-of-hospital emergency care physician, the patient ingested 200 tablets, each containing 200 mg of caffeine, mixed with an energy drink. The medical history revealed suicidal ideation and one previous suicide attempt involving alcohol and diazepam ingestion. Symptoms associated with intoxication included sinus tachycardia with a heart rate of 140/min without hemodynamic compromise, profuse vomiting of dark-colored content, and agitation. Further physical examination revealed no additional abnormalities. The patient also reported a sore throat, upper limb pain, palpitations and nausea. The initial electrocardiogram demonstrated sinus tachycardia without ST-segment or T-wave abnormalities. Initial laboratory tests demonstrated leukocytosis (14.1x109 L), hypokalemia (2.3 mmol/L) and arterial blood gas findings consistent with respiratory alkalosis and concomitant metabolic acidosis (pH 7.473; P_aCO_2 2.18 kPa, HCO_3^- 10 mmol/L; base excess -9 mmol/L). Mildly elevated liver enzymes (AST 65-128 IU/L; ALT 57 IU/L) and D-dimers (746 mg/L) were noted. Creatine kinase (CK) levels were markedly elevated. The patient was initially treated with symptomatic and supportive therapy, including intravenous crystalloid and diazepam administration (10 mg in 500 ml of 0.9% NaCl solution), as well as intravenous potassium replacement (30 mEq KCl). Nasogastric tube placement was attempted to facilitate gastrointestinal decontamination; however, it was unsuccessful due to patient's psychomotor agitation. An increasing trend of CK (500 IU/L to 5317 IU/L) suggested rhabdomyolysis, in the context of intoxication and psychomotor agitation. Therefore, requiring monitoring of renal and cardiac function, he was admitted to the intensive care unit (ICU).

The key events during the patient's clinical course are summarized in Table 1.

Serum creatinine remained within the reference range (74-89 mmol/L) throughout hospitalization, and the patient did not meet KDIGO criteria for acute kidney injury. Initially, the patient was psychotic with expressed suicidal intent. Later during hospitalization, he was cooperative, with correction of metabolic parameters, cessation of vomiting and rhythm stabilization. Continuous cardiac monitoring was performed throughout the three-day ICU stay, and no malignant arrhythmias or conduction abnormalities were documented. Improvement in somatic condition and hemodynamic stabilization were observed. Following regression of relevant laboratory parameters under conservative therapy, the patient was discharged and referred for further treatment at a psychiatric institution. Adequate fluid intake was emphasized among recommendations.

Table 1. Timeline of the clinical course

Time	Event
0 h	Caffeine ingestion
4:30 h	ED presentation
12h	CK increase; ICU admission
96 h	Discharge

Discussion

Clinical presentation of acute caffeine intoxication is characterized by a broad spectrum of symptoms, from sympathomimetic ones to serious cardiovascular and metabolic complications (1,2). The most frequently described early symptoms are severe vomiting and hypokalemia which may serve as diagnostic clues (2). Although our patient presented with tachycardia without hemodynamic compromise, literature suggests more critical presentations (2,4,5). In the case reported by Harsten et al., polymorphic ventricular tachycardia and dangerous acid-base disturbances occurred after 20 g of caffeine ingestion (4). Mitomo et al. described supraventricular tachycardia with a heart rate of more than 240/min following ingestion of 9.8 g of caffeine (5). Delayed absorption, emesis, genetic differences and early treatment may result in heterogeneous clinical outcomes (2). Although the reported ingested dose was approximately 40 g of caffeine, the clinical course was considerably milder than expected. Factors such as repeated emesis with incomplete gastrointestinal absorption, delayed gastric emptying, uncertainty regarding the reported dose and interindividual variability in caffeine pharmacokinetics may explain this discrepancy. Therefore, the reported ingested dose should be interpreted cautiously to avoid underestimating the potentially lethal toxicity of massive caffeine overdose (1,2).

Supportive therapy remains the cornerstone of caffeine intoxication management.

While gastrointestinal decontamination should be considered after potentially life-threatening caffeine ingestion, its application may be limited by agitation and inability to maintain nasogastric access (1,2). Increased muscle activity caused by excessive catecholamine release and psychomotor agitation may lead to muscle injury (2,3). Rhabdomyolysis has been described in about 10% of cases of caffeine intoxication and may lead to acute kidney injury. In this case report, the patient did not develop renal complications, despite CK levels exceeding 5000 IU/L, likely due to prompt initiation of supportive therapy. Serial creatine kinase monitoring should be performed in patients with severe caffeine intoxication, even in the absence of malignant arrhythmias or acute kidney injury, as early recognition of rhabdomyolysis allows timely supportive treatment and may prevent renal complications (1,2,6).

Hemodialysis should be considered in life-threatening caffeine intoxication.

Treatment of acute caffeine intoxication remains supportive and is based on fluid replacement, correction of electrolyte disbalances and cardiac monitoring. In contrast to the favorable outcome of supportive therapy in our patient, several cases required hemodialysis (7,8). In hemodynamically stable patients, conservative therapy may be adequate; however close clinical and laboratory monitoring is essential due to potential life-threatening complications (1,7,8). Recent studies suggest that the largest proportion of severe caffeine intoxication cases resulted from intentional self-poisoning. The second-largest proportion was due to accidental consumption. Ingestion of caffeine with suicidal intent occurs mostly among young adults with underlying psychiatric disorders (1,9).

Reported ingested doses should be interpreted cautiously, as absorption may vary.

Conclusion

Caffeine intoxication may present with a wide range of clinical symptoms, followed by potentially severe systemic complications, such as malignant arrhythmias and acute kidney injury. This case highlights the need for close clinical observation and awareness of less common manifestations, specifically rhabdomyolysis. Early supportive therapy remains crucial when managing intoxicated patients, as well as psychiatric evaluation in cases of intentional overdose.

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CASE REPORT / PRIKAZ SLUČAJA

WALKING AND TALKING WITH A pH OF 6.93: ACUTE KIDNEY INJURY MISSED IN A RESOURCE-LIMITED EMERGENCY SETTING

HODA I RAZGOVARA S pH 6,93: PREVID AKUTNE OZLJEDE BUBREGA U HITNOJ MEDICINSKOJ SLUŽBI S OGRANIČENIM RESURSIMA

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Abstract

Background: Acute kidney injury may present with nonspecific symptoms, particularly in elderly patients. Limited diagnostic resources in remote areas can delay the correct diagnosis and recognition of life-threatening conditions, including metabolic disturbances.

Case report: An eighty-year-old woman presented to a remote emergency department with fatigue and mild dyspnea. There were no available point-of-care (PoC) devices and she was referred to a tertiary center where she was diagnosed with acute kidney injury and severe metabolic disturbances. After initial management, she was subsequently enlisted in a chronic hemodialysis program.

Discussion: Acute kidney injury is often under-recognized early due to asymptomatic or nonspecific presentation, especially in elderly patients. Serum creatinine is a delayed marker, PoC testing for acid-base parameters can signal acute kidney injury before creatinine rises. In remote settings, integrating PoC testing for creatinine, urine biomarkers, and blood gas/acid-base analyzers may reduce diagnostic delay. Metabolic disturbances like severe acidosis themselves raise acute kidney injury suspicion, making PoC acid-base testing a valuable adjunct in remote emergency care.

Conclusion: Severe metabolic derangements may present with mild, nonspecific symptoms, particularly in elderly patients. This case also highlights the importance of prompt access to PoC devices in remote settings to enable early recognition, appropriate referral, and timely treatment.

Keywords: Dyspnea; Acute kidney injury; Acidosis; Hyperkalemia; Hemodialysis; Point-of-care devices.

Sažetak

Uvod: Akutno oštećenje bubrega može se očitovati nespecifičnim simptomima, osobito u starijih bolesnika. Ograničene dijagnostičke mogućnosti u udaljenim područjima mogu odgoditi pravodobno postavljanje dijagnoze i prepoznavanje životno ugrožavajućih stanja, uključujući metaboličke poremećaje.

Prikaz slučaja: Osamdesetogodišnja bolesnica javila se u udaljenu hitnu službu zbog umora i blage dispneje. Uređaji za dijagnostiku uz bolesnika (engl. *point-of-care*, PoC) nisu bili dostupni te je bolesnica upućena u tercijarni centar, gdje su dijagnosticirani akutno oštećenje bubrega te teški metabolički poremećaji. Nakon početnog liječenja uključena je u program kronične hemodijalize.

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Rasprava: Akutno oštećenje bubrega često se ne prepoznaje u ranoj fazi zbog asimptomatske ili nespecifične kliničke slike, osobito u starijih bolesnika. Budući da porast koncentracije serumskog kreatinina kasni, PoC određivanje acidobaznih pokazatelja može upozoriti na akutno oštećenje bubrega prije porasta kreatinina. U udaljenim sredinama uvođenje PoC određivanja kreatinina i bioloških pokazatelja u mokraći te analizatora krvnih plinova i acidobaznog statusa može smanjiti dijagnostičko kašnjenje. Metabolički poremećaji poput teške acidoze sami po sebi pobuđuju sumnju na akutno oštećenje bubrega, zbog čega je PoC analiza acidobaznog statusa vrijedan dodatak hitnom zbrinjavanju u udaljenim područjima.

Zaključak: Teški metabolički poremećaji mogu se očitovati blagim i nespecifičnim simptomima, osobito u starijih bolesnika. Ovaj slučaj također naglašava važnost pravodobne dostupnosti PoC uređaja u udaljenim sredinama radi ranog prepoznavanja bolesti, odgovarajućeg upućivanja i pravodobnog liječenja.

Ključne riječi: acidoza; akutno oštećenje bubrega; dispneja; hemodijaliza; hiperkalemija; uređaji za dijagnostiku uz bolesnika

Introduction

Acute kidney injury is an abrupt decline in renal function that carries high morbidity and mortality, particularly when recognition and treatment are delayed. Clinically, acute kidney injury is defined by increases in serum creatinine and/or reduced urine output. However, creatinine is a delayed marker that may rise only after substantial kidney injury has occurred, and urine output can be difficult to monitor reliably outside institutional settings.

> Acute kidney injury is a rare but potentially life-threatening condition. Elderly patients with severe acute kidney injury may present with minimal or no symptoms.

The most common cause of acute kidney injury in elderly patients is prerenal due to dehydration, accounting for 43% of cases in patients over 65 years compared to 29% in younger patients (1). Renal hypoperfusion accounts for 68.8% of acute kidney injury cases outside the intensive care unit. The most frequent comorbidities are hypertension, chronic kidney disease, coronary artery disease, diabetes, and heart failure. Most common triggers are diarrhea, infections, acute heart failure, dehydration and hypotension (2). Early manifestations are often nonspecific-fatigue, dyspnea, and subtle changes in mental status-and may be overlooked in elderly patients or those with chronic comorbidities (3). Without prompt diagnosis and supportive care, acute kidney injury can progress rapidly to severe metabolic derangements, including life-threatening hyperkalemia and profound metabolic acidosis (4).

In remote or resource-limited settings, the absence of basic laboratory diagnostics further delays recognition and appropriate referral. Point-of-care (PoC) testing could enable decentralized diagnostic analysis by offering portability, automation, and the ability to deliver results more quickly and at lower cost. Common PoC devices include those for blood glucose, pregnancy testing, blood gas and electrolyte analysis, urine testing, bacterial screening, and forensic medicine applications (5).

> Integrating PoC blood gas analysis into clinical pathways in remote settings may provide a critical diagnostic bridge, enabling earlier recognition of severe metabolic disturbances and prompting timely transfer and treatment.

Case presentation

An eighty-year-old woman presented to a remote emergency department with fatigue and mild dyspnea. She was undergoing treatment for scabies associated with troublesome sleeping and reduced oral intake the preceding week. The patient medical history included arterial hypertension, type 2 diabetes mellitus and hyperlipidemia. Examination was unremarkable with normal vital parameters and electrocardiogram. There was no available PoC devices and no available laboratory or imaging testing in surrounding area. Given her age and acute treatment of scabies, she was discharged as likely exhaustion and sleep deprivation, with instructions to return/call if her condition aggravates or doesn't improve. Upon re-presentation with persistent symptoms two days later, she was referred to tertiary center. At admission at the hospital, she was hemodynamically stable. Arterial blood gas revealed severe metabolic acidosis and laboratory findings presented acute kidney injury and increased potassium levels (Table 1.)

Initial management included calcium gluconate, insulin with glucose, furosemide, and sodium bicarbonate followed by urgent hemodialysis at the intensive unit. She was subsequently initiated in a chronic hemodialysis program. A chronological summary of key events of this case is presented in Table 2.

Table 1. Arterial blood gas and laboratory results indicating metabolic acidosis and acute kidney injury.

pH	6.93
cBase	-26.8
pCO2 (kPa)	2.06
HCO3 (mmol/L)	5.2
eGFR (ml/min/1.73m²)	2.4
Creatinine (µmol/L)	1145
Urea (mmol/L)	53
K⁺ (mmol/L)	7.1

Table 2. Timeline of the patient's clinical course

Time	Clinical event
Day −7	Scabies diagnosis and initiation of treatment
Days −7 to 0	Poor sleep and reduced oral intake
Day 0	Initial patient contact and examination
Day 2	Re-presentation and referral to the tertiary center; hospital admission, initial management, and emergency hemodialysis
Day 3+	Enrollment in a chronic hemodialysis program

Discussion

Acute kidney injury is frequently under-recognized in its early stages, as many patients with mild to moderate disease remain asymptomatic and are identified only after laboratory testing (4). When symptoms do occur, they are often nonspecific: nausea or vomiting (33.3%), dyspnea (14.5%), oliguria (16.2%), and confusion (6.8%), while up to 31.6% of patients may remain asymptomatic, which can delay recognition particularly in elderly individuals with multiple comorbidities (3).

In the present case, despite a pH of 6.93 and bicarbonate level of 5.2 mmol/L, the patient remained hemodynamically stable and presented only with fatigue and mild dyspnea. This marked discordance between biochemical severity and clinical presentation highlights how advanced metabolic derangements may remain clinically subtle and contribute to delayed recognition of critical illness.

Serum creatinine, although central to diagnosis, is a delayed marker of decreased glomerular filtration rate and may require 24–72 hours to reach a new steady state following acute kidney injury, thereby postponing detection of clinically significant renal dysfunction (6). While PoC creatinine testing is not yet sufficiently validated to replace standard laboratory measurements (7), PoC blood gas analysis may offer a practical and reliable alternative for early detection of metabolic disturbances. PoC blood gas analysis can rapidly assess acid-base status and selected hematologic, metabolic, and electrolyte parameters (pH, pO_2, pCO_2, hematocrit, hemoglobin, sodium, potassium, chloride, ionized calcium, ionized magnesium, glucose, lactate, anion gap and some other parameters depending on the device model) (8). Among these, pH, pCO_2, and bicarbonate levels are particularly useful for identifying severe metabolic acidosis, which may serve as an early indicator of acute kidney injury (9).

> Severe metabolic acidosis may be an early indicator of acute kidney injury before serum creatinine rises.

This has potential to be of importance in remote emergency settings, such as in this case, where the nearest tertiary center was over one hour away and advanced transport options were limited. Severe acidosis could have raised suspicion of acute kidney injury and justified urgent escalation of care. In such environments, the absence of diagnostic tools, including laboratory testing and PoC devices, possibly increases the risk of delayed diagnosis and referral.

Conclusion

Acute kidney injury in elderly patients may present with minimal symptoms despite severe metabolic derangement and normal vital signs. In this remote emergency case, the absence of laboratory diagnostics and PoC testing delayed recognition of acute kidney injury and life-threatening acidosis. PoC blood gas analysis may help identify critical metabolic abnormalities earlier, guide initial supportive treatment, and support timely referral in remote emergency settings.

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CASE REPORT / PRIKAZ SLUČAJA

VALPROATE-INDUCED HYPERAMMONEMIC ENCEPHALOPATHY

VALPROATOM UZROKOVANA HIPERAMONEMIJSKA ENCEFALOPATIJA

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Abstract

Background: Valproate is a broad-spectrum antiepileptic drug. Valproate-induced hyperammonemic encephalopathy is an uncommon but serious adverse effect of valproate therapy.

Case presentation: We present the case of a 33-year-old woman on long-term valproate therapy who was admitted to the emergency department due to progressive impairment of consciousness. She had pharmacoresistant epilepsy and alcohol use disorder. Workup excluded structural, infectious, and psychiatric causes. Electroencephalography showed diffuse slowing of background activity consistent with generalized encephalopathy. Routine laboratory tests, including liver function, were within the normal range. Plasma ammonia was elevated. In the context of ongoing valproate use, normal liver function, and elevated ammonia, valproate-induced hyperammonemic encephalopathy was suspected. Valproate dosage was reduced and lactulose was initiated. Ammonia levels gradually decreased, accompanied by complete clinical recovery and return to baseline neurological status.

Conclusion: This case highlights that any sudden change in mental status in a patient receiving valproate should raise suspicion for valproate-induced hyperammonemic encephalopathy, enabling prompt diagnosis and timely treatment.

Keywords: encephalopathy; hyperammonemia; valproate.

Sažetak

Uvod: Valproat je antiepileptik širokog spektra. Hiperamonemijska encefalopatija rijedak je, ali ozbiljan neželjeni učinak terapije valproatom.

Prikaz slučaja: Prikazujemo slučaj 33-godišnje žene na dugotrajnoj terapiji valproatom koja je primljena na hitni bolnički prijam zbog progresivnog poremećaja svijesti. Bolovala je od farmakorezistentne epilepsije i ovisnosti o alkoholu. Dijagnostičkom obradom isključeni su strukturni, infektivni i psihijatrijski uzroci. Elektroencefalografija je pokazala difuzno usporenje moždane aktivnosti u skladu s generaliziranom encefalopatijom. Rutinski laboratorijski nalazi, uključujući funkciju jetre, bili su unutar normalnih granica. Razina amonijaka u plazmi bila je povišena. S obzirom na kontinuiranu primjenu valproata, normalnu funkciju jetre i povišeni amonijak, posumnjalo se na valproatom uzrokovanu hiperamonemijsku encefalopatiju. Doza valproata je smanjena, a uvedena je laktuloza. Vrijednosti amonijaka postupno su se snižavale, uz potpuni oporavak svijesti i povratak na početnu neurološku funkciju.

Zaključak: Ovaj slučaj naglašava da svaka nagla promjena mentalnog statusa u bolesnika na terapiji valproatom treba pobuditi sumnju na valproatom uzrokovanu hiperamonemijsku encefalopatiju, što omogućuje pravodobnu dijagnozu i liječenje.

Ključne riječi: encefalopatija; hiperamonemija; valproat.

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Introduction

Valproate is commonly prescribed for epilepsy, bipolar disorder, and various psychiatric conditions. While generally regarded as safe, valproate has been linked to several adverse effects, including hepatotoxicity, pancreatitis, thrombocytopenia, and hyperammonemia. Hyperammonemia frequently occurs during valproate therapy; however, progression to valproate-induced hyperammonemic encephalopathy (VHE) is rare but can be life-threatening (1).

The pathophysiology of VHE is not fully understood. Current evidence indicates that valproate disrupts the urea cycle by inhibiting key enzymes responsible for ammonia metabolism, leading to elevated serum ammonia levels. This accumulation of ammonia in the central nervous system increases cerebral glutamine production, causes astrocyte swelling, and results in cerebral edema, which ultimately leads to neurological dysfunction (2,3).

Hyperammonemic encephalopathy is a rare but potentially life-threatening adverse effect of valproate.

Clinical manifestations of VHE range from mild cognitive impairment and lethargy to confusion, altered mental status, vomiting, focal neurological deficits, increased seizure frequency, and, in severe cases, coma. Because these symptoms are often nonspecific and may resemble the progression of underlying neurological or psychiatric disorders, clinicians should consider VHE in any patient receiving valproate who presents with unexplained changes in mental status (1,4). We report a case of VHE in a patient receiving valproate therapy who achieved complete clinical recovery.

Altered mental status in patients receiving valproate should prompt ammonia testing.

Case presentation

A 33-year-old woman presented to our emergency department (ED) with progressive impairment of consciousness. According to family members, she became increasingly somnolent over 3 days prior to admission and was soporous on the day of presentation. There was no reported history of recent seizures, head trauma, fever, or clinical signs of infection.

She had a history of pharmacoresistant epilepsy, which was initially diagnosed as juvenile myoclonic epilepsy and was later complicated by posttraumatic structural epilepsy after traumatic brain injury. She was also receiving psychiatric care for alcohol use disorder. Her long-term antiseizure regimen consisted of valproate (500 mg in the morning and 750 mg in the evening), levetiracetam (1000 mg twice daily), and zonisamide (75 mg twice daily). Concomitant psychotropic medications included escitalopram, diazepam, mirtazapine, and quetiapine. Topiramate was not included in her treatment regimen. Given her psychiatric history, an acute psychiatric decompensation was initially considered; however, psychiatric evaluation did not support a primary psychiatric etiology.

Neurological examination revealed a quantitative disturbance of consciousness, characterized by marked somnolence, without focal neurological deficits. An urgent diagnostic workup was performed. Non-contrast brain computed tomography showed no acute intracranial pathology. Electroencephalography demonstrated diffuse slowing of background activity, predominantly in the bilateral frontotemporal regions, consistent with a generalized encephalopathic process. Routine laboratory investigations, including complete blood count, serum electrolytes, renal function tests, and inflammatory markers, were within normal limits. Liver function tests were also within the reference range (aspartate aminotransferase (AST) 32 U/L, alanine aminotransferase (ALT) 40 U/L, gamma-glutamyl transferase (GGT) 43 U/L, alkaline phosphatase (ALP) 112 U/L, and total bilirubin 12 μmol/L). Given the patient's history of chronic alcohol use, plasma ammonia levels were measured and found to be elevated (151 μmol/L; reference range 18 - 72 μmol/L). In the context of ongoing valproate therapy, normal liver function, elevated plasma ammonia, and electroencephalographic findings suggestive of metabolic encephalopathy, VHE was suspected. The patient was admitted to the neurology department for further management. Valproate dosage was reduced, but not discontinued due to pharmacoresistant epilepsy, and lactulose therapy was initiated to enhance ammonia elimination. Levocarnitine was not administered. Plasma ammonia levels gradually decreased to 73 μmol/L on hospital day 2.57 μmol/L on day 4, and 65 μmol/L on day 8, accompanied by complete clinical recovery and return to baseline neurological status. Based on the clinical presentation, exclusion of alternative etiologies, elevated plasma ammonia, and favorable response to valproate dose reduction and ammonia-lowering therapy, a diagnosis of VHE was established.

Discussion

Valproate-induced hyperammonemic encephalopathy (VHE) is a significant adverse effect of valproate therapy that may occur more often than is generally recognized. Valproate-associated hyperammonemia is thought to be uncommon but has been reported with widely varying incidence rates. Overt encephalopathy may occur with normal liver function tests and therapeutic serum valproate concentrations. Therefore, the diagnosis may be missed unless there is a high index of suspicion in patients developing an acute change in mental status during valproate therapy (1,4). The pathogenesis of VHE is not fully understood. There are several mechanisms involved and they are interrelated. Valproate may inhibit carbamoyl phosphate synthetase I and thus impair the urea cycle and reduce ammonia clearance. Other contributing factors

include the accumulation of toxic metabolites, mitochondrial dysfunction, and carnitine depletion, all of which may further promote hyperammonemia. The resulting elevation in ammonia induces neurotoxic effects, mainly through astrocytic glutamine accumulation, osmotic swelling, and cerebral edema. Electroencephalography in VHE typically shows generalized slowing or other diffuse encephalopathic patterns, consistent with a metabolic disturbance of cerebral function (1,5).

Several risk factors have been associated with VHE, including underlying urea cycle disorders, liver disease, concomitant antiepileptic therapy (particularly topiramate), fasting, poor nutritional status, and intellectual disability. Nevertheless, VHE may occur without identifiable predisposing factors and does not seem to correlate reliably with valproate dose, treatment duration, or serum drug level. This variability suggests that individual susceptibility plays an important role in its development (1,4).

Management is focused on reducing ammonia levels and withdrawal or reduction of valproate exposure. In general, valproate should be discontinued; however, dose reduction may be required in selected patients in whom seizure control must be maintained. Lactulose and levocarnitine are adjunctive therapies in common use (4,6,7). In the present case, levocarnitine was not administered because the patient demonstrated prompt clinical improvement following reduction of the valproate dose and initiation of lactulose therapy. In the absence of acute valproate overdose, hepatotoxicity, or progressive neurological deterioration, additional treatment with levocarnitine was not considered necessary.

Valproate dose reduction and lactulose therapy may be effective when valproate withdrawal is not an option.

In our patient, the diagnosis of VHE was based on subacute deterioration in consciousness, elevated plasma ammonia levels, preserved liver function, and electroencephalographic evidence of diffuse encephalopathy. The differential diagnosis was initially broadened by the patient's alcohol use disorder and psychiatric comorbidities; however, neuroimaging, laboratory evaluation, and psychiatric assessment did not support an alternative etiology. Although complete withdrawal of valproate was not feasible due to pharmacoresistant epilepsy, the time-related association between hyperammonemia, neurological deterioration, and subsequent improvement following valproate dose reduction and lactulose therapy, together with exclusion of alternative causes, strongly supports valproate as the most likely precipitating factor. Nonetheless, because valproate was reduced rather than fully discontinued, causal attribution remains partly inferential and cannot be established with absolute certainty.

Conclusion

VHE should be considered in any patient receiving valproate who presents with otherwise unexplained encephalopathy, even when liver function tests and serum valproate concentrations are within the normal range. Prompt recognition and timely intervention are essential to prevent serious neurological sequelae.

Patient confidentiality

The patient's confidentiality and anonymity were maintained throughout the preparation of this manuscript. No identifying personal information has been included.

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REVIEW ARTICLE / PREGLEDNI ČLANAK

PREHOSPITAL BLOOD PRODUCT ADMINISTRATION IN CIVILIAN EMERGENCY MEDICAL SYSTEMS: EVIDENCE, CONTROVERSIES, AND IMPLEMENTATION CHALLENGES

PRIMJENA KRVNIH PRIPRAVAKA U IZVANBOLNIČKOJ HITNOJ MEDICINSKOJ SLUŽBI U CIVILNIM SUSTAVIMA: DOKAZI, KONTROVERZE I IZAZOVI UVOĐENJ

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Abstract

Hemorrhagic shock remains a major preventable cause of trauma-related mortality, prompting increasing interest in prehospital blood product administration as a strategy for earlier hemostatic resuscitation. However, evidence supporting widespread implementation in civilian emergency medical systems (EMS) remains inconsistent. This review critically examines contemporary evidence regarding the effectiveness, feasibility, and limitations of prehospital blood product administration in civilian trauma care. While some studies suggest improved survival and physiological stabilization, others have failed to demonstrate meaningful benefit in mortality or major clinical outcomes, particularly in systems with short transport times. Interpretation of available evidence is further complicated by heterogeneity in patient populations, transport duration, and transfusion protocols. Current trauma and transfusion guidelines do not uniformly support routine prehospital blood product administration and generally advocate a selective, context-dependent approach. In addition to uncertain clinical benefit, implementation presents important logistical and organizational challenges, including storage requirements, cold-chain maintenance, traceability, and product wastage. Current evidence suggests that prehospital blood product administration may be most beneficial in carefully selected patients with severe hemorrhagic shock, prolonged transport intervals, or delayed access to definitive hemorrhage control.

Keywords: civilian trauma care; hemorrhagic shock; prehospital blood transfusion.

Sažetak

Hemoragijski je šok i dalje jedan od glavnih sprječivih uzroka smrtnosti povezane s traumom, zbog čega raste interes za primjenu krvnih pripravaka u izvanbolničkim uvjetima kao strategiju ranijeg započinjanja hemostatske resuscitacije. Međutim, dokazi koji podupiru njezino široko uvođenje u civilne sustave hitne medicinske službe su i dalje neujednačeni. U ovom preglednom radu kritički se analiziraju suvremeni dokazi o učinkovitosti, izvedivosti i ograničenjima primjene krvnih pripravaka u izvanbolničkom zbrinjavanju traumatiziranih bolesnika. Dok neka istraživanja upućuju na poboljšano preživljenje i fiziološku stabilizaciju, druga nisu pokazala značajnu korist u pogledu smrtnosti ili drugih važnih kliničkih ishoda, osobito u sustavima s kratkim vremenom transporta. Tumačenje dostupnih dokaza dodatno je otežano heterogenošću populacija bolesnika, trajanjem transporta i transfuzijskim protokolima. Aktualne smjernice za zbrinjavanje traume i transfuzijsko liječenje ne podupiru jednoznačno rutinsku primjenu krvnih pripravaka u izvanbolničkim uvjetima te uglavnom zagovaraju selektivan pristup prilagođen okolnostima. Uz neizvjesnu kliničku

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korist, uvođenje takve prakse povezano je sa značajnim logističkim i organizacijskim izazovima, uključujući zahtjeve za skladištenjem, održavanje hladnog lanca, sljedivost i neiskorištavanje odnosno otpis krvnih pripravaka. Trenutačni dokazi upućuju na to da bi primjena krvnih pripravaka u izvanbolničkim uvjetima mogla biti najkorisnija u pažljivo odabranih bolesnika s teškim hemoragijskim šokom, produljenim vremenom transporta ili odgođenim pristupom definitivnoj kontroli krvarenja.

Ključne riječi: civilno zbrinjavanje traumatiziranih bolesnika; hemoragijski šok; izvanbolnička transfuzija krvi

Introduction

Uncontrolled hemorrhage remains a major contributor to preventable trauma-related mortality, particularly during the early post-injury period (1–3). Conventional trauma resuscitation strategies have historically emphasized rapid transport to definitive care while relying primarily on crystalloid administration during the prehospital phase (2). However, increasing recognition of trauma-induced coagulopathy (TIC), the dilutional effects of excessive crystalloid use, and the importance of early hemostatic resuscitation has prompted renewed interest in prehospital blood product administration (4,5). Military experience, particularly from contemporary combat settings, demonstrated encouraging results associated with early transfusion strategies, including reduced mortality and improved physiological stabilization among severely injured patients with hemorrhagic shock (6). These observations stimulated growing interest in translating similar approaches into civilian emergency medical systems (EMS), particularly within physician-led retrieval teams, helicopter emergency medical services (HEMS), and remote or rural trauma networks (7,8).

Despite increasing implementation across selected EMS systems, an important question remains unresolved: is prehospital blood product administration truly justified in civilian medicine, or has implementation advanced faster than supporting evidence? Although several studies suggest potential benefit in selected high-risk populations, findings remain inconsistent and highly dependent on transport duration, patient selection, severity of shock, and healthcare system organization (9,10). Importantly, the clinical question is no longer whether prehospital blood product administration can improve outcomes under ideal circumstances, but rather under which conditions, in which patients, and within which EMS systems such interventions provide meaningful benefit sufficient to justify operational complexity and resource allocation. This distinction is particularly relevant for European civilian EMS models characterized by relatively short transport intervals and rapid access to definitive hospital care.

Prehospital blood product administration may benefit selected patients with severe hemorrhagic shock, but its role in civilian EMS remains dependent on patient selection, transport time, system organization, and available evidence.

The aim of this review is to critically examine the current evidence regarding prehospital blood product administration in civilian trauma care, with particular emphasis on randomized evidence, observational studies, logistical feasibility, and the balance between potential clinical benefit and practical implementation challenges.

Pathophysiological rationale for early blood product administration

The theoretical rationale for prehospital blood product administration is grounded in the time-sensitive nature of traumatic hemorrhage and the early physiological derangements that emerge following severe injury. Hemorrhagic shock is not merely a consequence of progressive blood loss but a dynamic process characterized by impaired tissue perfusion, oxygen debt, metabolic acidosis, endothelial dysfunction, systemic inflammation, and the rapid development of trauma-induced coagulopathy (TIC) (2,11,12). Importantly, many of these processes begin during the prehospital phase, often before definitive hemorrhage control can be achieved, suggesting that clinically relevant physiological deterioration may already be underway prior to hospital arrival.

Trauma-induced coagulopathy represents one of the earliest and most clinically relevant therapeutic targets in trauma care. Historically regarded primarily as a dilutional consequence of blood loss and fluid resuscitation, TIC is now increasingly recognized as an endogenous and multifactorial process initiated shortly after injury and driven by tissue trauma, hypoperfusion, endothelial dysfunction, inflammation, platelet dysfunction, and dysregulated fibrinolysis (13). Early coagulopathy has consistently been associated with increased transfusion requirements, multiple organ dysfunction, and substantially higher mortality among severely injured trauma patients (13,14).

Trauma-induced coagulopathy develops early after severe injury, supporting the rationale for initiating hemostatic resuscitation before hospital arrival.

The early onset of TIC raises an important therapeutic question: should hemostatic interventions begin before hospital arrival? If coagulopathy is already evolving during transport, delayed correction following emergency department admission may

represent a missed therapeutic opportunity. Consequently, early administration of plasma, fibrinogen-containing products, packed red blood cells (PRBCs), or low-titer group O whole blood (LTOWB) has emerged as a biologically plausible strategy aimed not only at restoring circulating volume but also at simultaneously supporting oxygen delivery and coagulation during the earliest phases of hemorrhagic shock (9, 14,16).

Historically, prehospital trauma resuscitation emphasized rapid crystalloid administration to restore intravascular volume and maintain systemic blood pressure until definitive hemorrhage control could be achieved. However, this paradigm has increasingly been challenged. Excessive crystalloid administration may contribute to dilutional coagulopathy, worsening acidosis and hypothermia, endothelial glycocalyx disruption, tissue edema, and impaired oxygen delivery while failing to replace clotting factors or oxygen-carrying capacity (2,5,15). Furthermore, aggressive fluid resuscitation prior to hemorrhage control may increase intravascular hydrostatic pressure, disrupt early clot stability, and potentially exacerbate ongoing bleeding, particularly in patients with uncontrolled hemorrhage (15).

Recognition of these limitations contributed to a paradigm shift toward *damage control resuscitation* and *hemostatic resuscitation* strategies, which prioritize rapid hemorrhage control, permissive hypotension in selected patients, minimization of crystalloid exposure, and balanced replacement of blood components (16). Within this framework, prehospital blood product administration has been proposed as a strategy to attenuate progression of hemorrhagic shock before hospital arrival. The biological rationale is compelling: early blood product administration may restore oxygen-carrying capacity, preserve intravascular volume, attenuate coagulopathy, improve tissue perfusion, and potentially mitigate secondary physiological deterioration during transport.

Nevertheless, biological plausibility alone is insufficient to justify widespread implementation of a complex and resource-intensive intervention. The key question remains whether these theoretical benefits translate into clinically meaningful improvements in outcomes within civilian emergency medical systems, where transport times, trauma epidemiology, logistics, and organizational structures differ substantially from military settings. Determining whether prehospital blood product administration improves survival, reduces transfusion requirements, or attenuates trauma-induced physiological deterioration in civilian trauma populations therefore remains an important area of ongoing investigation.

Clinical evidence for prehospital blood product administration

Despite strong pathophysiological rationale supporting early hemostatic resuscitation, clinical evidence regarding the effectiveness of prehospital blood product administration in civilian trauma care remains inconsistent. Over the past decade, several randomized controlled trials, observational cohort studies, and registry analyses have attempted to determine whether early transfusion strategies improve survival and physiological outcomes in patients with traumatic hemorrhagic shock. However, interpretation of available evidence remains challenging because of substantial heterogeneity in study design, patient selection, transport duration, injury severity, and the type of blood products administered.

Among the most influential randomized investigations, Sperry et al. reported an association between prehospital plasma administration and lower 30-day mortality among severely injured trauma patients transported by helicopter over prolonged distances (9). Patients at risk of hemorrhagic shock who received thawed plasma during transport experienced lower mortality compared with standard care. Importantly, the observed benefit appeared greatest among patients with prolonged transport intervals and more severe physiological derangement, suggesting that timing of hemostatic intervention may be clinically relevant (9).

In contrast, Moore et al. failed to demonstrate a mortality benefit from prehospital plasma administration in an urban emergency medical system characterized by relatively short transport intervals (17). Although plasma administration was feasible and safe, no significant differences were observed in mortality or major clinical outcomes between intervention and standard care groups. These findings raised important questions regarding the influence of transport duration and healthcare system organization on the effectiveness of prehospital blood product administration, suggesting that benefit may be context-dependent rather than universal (17).

Similarly, Crombie et al. evaluated prehospital administration of packed red blood cells and lyophilized plasma compared with standard crystalloid resuscitation in trauma patients at risk of hemorrhagic shock and failed to demonstrate significant improvement in the primary composite outcome of mortality or lactate clearance (18). Although some physiological benefits were observed, interpretation of these findings was complicated by heterogeneity in injury severity, variability in timing of intervention, and relatively short transport intervals within participating trauma systems (18).

The benefit of prehospital blood product administration appears to be context-dependent, with greater potential benefit in patients with severe hemorrhagic shock, prolonged transport times, and delayed access to definitive hemorrhage control.

Taken together, randomized evidence does not uniformly support routine implementation of prehospital blood product administration across all civilian emergency medical systems. Rather, available findings suggest that effectiveness may depend on factors such as transport duration, severity

of hemorrhagic shock, timing of intervention, and patient selection. Importantly, studies conducted within systems characterized by rapid access to definitive trauma care have generally demonstrated less consistent benefit than those involving prolonged prehospital intervals (9, 17,18).

In addition to randomized evidence, several observational studies and trauma registry analyses have reported associations between prehospital blood product administration and improved hemodynamic stabilization, reduced markers of shock severity, and lower mortality among selected high-risk trauma populations (19,20). Military experience has also substantially influenced enthusiasm for early transfusion strategies, with multiple combat-based studies reporting improved survival among severely injured patients receiving blood products early in the resuscitative process (21,22). However, translation of these findings into civilian systems remains challenging because of substantial differences in injury mechanisms, evacuation times, resource availability, and organizational structure.

More recently, growing interest has focused on the prehospital use of low-titer group O whole blood, which may offer both physiological and logistical advantages compared with conventional component therapy. By simultaneously providing red blood cells, plasma, and platelets in a single product, whole blood more closely approximates balanced hemostatic resuscitation while potentially simplifying transfusion logistics and reducing product complexity (23).

Observational studies have reported encouraging safety profiles and a potential survival benefit associated with low-titer group O whole blood use in selected trauma populations, although high-quality randomized evidence remains limited and important questions regarding patient selection, storage logistics, and comparative effectiveness remain unresolved (22,23)

Overall, current evidence suggests that prehospital blood product administration may confer clinically meaningful benefit in carefully selected trauma patients, particularly those with severe hemorrhagic shock, prolonged transport intervals, or delayed access to definitive hemorrhage control. Nevertheless, findings remain heterogeneous and insufficient to support universal implementation across all civilian emergency medical systems. Consequently, the question has increasingly shifted from whether prehospital blood products should be administered to under which conditions, in which patients, and within which systems such interventions provide sufficient benefit to justify operational complexity and resource utilization.

Current guideline perspective, implementation challenges, and future directions

Despite increasing interest and implementation of prehospital blood product administration in selected EMS systems, current international guidelines do not recommend its routine use in civilian trauma care. The available evidence is characterized by substantial heterogeneity in study design, patient selection, transport duration, healthcare system organization, and transfusion protocols, making universal recommendations difficult (2,4,5).

This uncertainty is reflected in contemporary international trauma guidelines. Importantly, no major contemporary guideline currently recommends routine prehospital blood product administration for all civilian trauma patients. The most recent European guideline on the management of major bleeding and coagulopathy following trauma recognizes the potential role of prehospital blood product administration within the concept of damage control resuscitation but does not recommend its routine use in civilian prehospital care because the available evidence remains limited and heterogeneous (2). Likewise, the recent Position Statement and Resource Document of the National Association of EMS Physicians (NAEMSP) emphasizes early recognition of life-threatening hemorrhage, minimization of excessive crystalloid administration, and rapid transport to definitive care, while acknowledging that evidence supporting universal prehospital transfusion strategies is still insufficient (5). Similarly, the most recent systematic review and clinical practice guideline update concluded that current data do not justify routine implementation and highlighted the need for further high-quality studies before stronger recommendations can be made (4).

Logistical barriers, including cold-chain maintenance, product availability, wastage, traceability, and coordination with transfusion services remain major challenges to widespread civilian implementation.

Consequently, the major challenge is no longer determining whether blood products can be administered safely in the prehospital environment, but rather identifying the patients and healthcare systems in which such an approach provides meaningful clinical benefit. Patients with severe hemorrhagic shock, prolonged transport intervals, remote geographical locations, or delayed access to definitive hemorrhage control appear to be the most plausible candidates; however, reliable tools for their early identification remain limited (9,17,18). Implementation also requires considerable logistical and organizational resources. Maintaining an uninterrupted cold chain, ensuring product availability, minimizing wastage, guaranteeing traceability, and coordinating transfusion services with emergency medical systems all represent substantial operational challenges. These factors may significantly influence the cost-effectiveness and feasibility of widespread implementation, particularly in civilian EMS systems characterized by short transport times and rapid access to trauma centers (4,5).

Growing interest in low-titer group O whole blood may partially overcome some of these limitations by simplifying transfusion logistics and providing balanced hemostatic

resuscitation through a single product. Nevertheless, important questions regarding optimal patient selection, storage protocols, comparative effectiveness, and economic sustainability remain unanswered (6,22,23).

Therefore, the current debate is no longer whether prehospital blood product administration is biologically plausible, but whether sufficient clinical evidence exists to justify its routine implementation in civilian emergency medical systems. At present, both the available evidence and contemporary guidelines support a selective, individualized, and system-dependent approach rather than universal adoption.

Importantly, this position is reinforced by the most recent randomized trials published in 2026, which have not demonstrated a clear clinical benefit of prehospital whole blood transfusion. The SWiFT trial (24) showed that, among patients with life-threatening hemorrhage, prehospital transfusion of two units of whole blood was not superior to standard care in reducing the risk of death or massive transfusion within 24 hours. Similarly, the TOWAR trial (25) found that, in injured patients with hemorrhagic shock, the use of whole blood for prehospital transfusion did not result in lower 30-day mortality compared with blood component therapy. Several factors may explain the neutral findings observed in these trials. Both studies included heterogeneous trauma populations treated within mature trauma systems, where relatively short transport intervals and rapid access to definitive care may have reduced the opportunity for prehospital transfusion to influence clinical outcomes. These findings therefore do not necessarily exclude a benefit in carefully selected patients experiencing prolonged transport or delayed hemorrhage control. These contemporary findings further suggest that, despite a strong biological rationale and encouraging observational data, current evidence does not support the routine universal implementation of prehospital blood product administration. Future research should therefore focus on identifying the patients most likely to benefit, optimizing transfusion strategies, and determining the organizational settings in which prehospital blood product administration provides clinically meaningful and cost-effective improvements in outcomes (2,4,5).

Conclusion

Prehospital blood product administration represents a promising strategy for the early management of traumatic hemorrhagic shock and is supported by a strong pathophysiological rationale. However, current clinical evidence remains heterogeneous and does not support its routine implementation across all civilian emergency medical systems. Moreover, the most recent randomized trials published in 2026 have also failed to demonstrate a clear clinical benefit of prehospital whole blood transfusion, further emphasizing the uncertainty regarding its universal use. Contemporary guidelines therefore advocate a selective, individualized, and system-dependent approach rather than routine implementation. Future research should focus on identifying the patients most likely to benefit, optimizing transfusion strategies, and determining the healthcare systems and organizational settings in which prehospital transfusion provides clinically meaningful, logistically feasible, and cost-effective improvements in outcomes. Until such evidence becomes available, a selective and evidence-based implementation tailored to local resources and patient populations appears to be the most appropriate strategy for civilian emergency medical systems.

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REVIEW ARTICLE / PREGLEDNI ČLANAK

DIGITAL COGNITIVE OVERLOAD IN THE EMERGENCY DEPARTMENT: IMPACT ON CLINICAL PERFORMANCE AND PATIENT SAFETY

DIGITALNA KOGNITIVNA PREOPTEREĆENOST U HITNOM BOLNIČKOM PRIJAMU: UTJECAJ NA KLINIČKU IZVEDBU I SIGURNOST BOLESNIKA

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Abstract

The digitalization of healthcare systems has significantly transformed clinical work in emergency departments. Electronic documentation, patient monitoring systems, alarm systems, digital notifications and parallel team communication enable faster access to information, but simultaneously increase the cognitive burden on healthcare professionals. In emergency settings, where decisions must be made rapidly, often under conditions of uncertainty and incomplete information, an excessive number of digital stimuli may impair attention, slow down decision making and increase the risk of errors.

Digital cognitive overload refers to a state in which the volume of information, the number of concurrent tasks and frequent interruptions exceed an individual's capacity for effective information processing. This narrative review presents current knowledge on digital cognitive overload in emergency care, with a particular focus on its impact on clinical performance, patient safety and work organization. Special attention is given to the sources of digital burden, its effects on clinical decision making, the role of alarms and interruptions, and potential strategies for reducing cognitive load in everyday clinical practice.

Keywords: clinical decision making; digital cognitive overload; emergency department; interruptions; patient safety

Sažetak

Digitalizacija zdravstvenog sustava značajno je promijenila rad u hitnoj službi. Elektronička dokumentacija, monitori, alarmni sustavi, digitalne obavijesti i paralelna komunikacija unutar tima omogućuju brži pristup informacijama, ali istodobno povećavaju kognitivno opterećenje zdravstvenih djelatnika. U hitnoj službi, gdje se odluke donose brzo, često uz nepotpune informacije i visok stupanj nepredvidivosti, prevelik broj digitalnih podražaja može narušiti održavanje pažnje, usporiti donošenje odluka i povećati rizik pogrešaka. Digitalna kognitivna preopterećenost označava stanje u kojem količina informacija, broj istodobnih zadataka i učestalost prekida rada nadilaze sposobnost pojedinca da ih učinkovito obradi. Ovaj narativni pregled prikazuje suvremene spoznaje o digitalnoj kognitivnoj preopterećenosti u hitnoj službi, s naglaskom na njezin utjecaj na kliničku izvedbu, sigurnost bolesnika i organizaciju rada. Posebna pozornost posvećena je izvorima digitalnog opterećenja, posljedicama za donošenje odluka, ulozi alarma i prekida rada te mogućim strategijama smanjenja opterećenja u svakodnevnoj kliničkoj praksi.

Ključne riječi: digitalna kognitivna preopterećenost; hitna služba; kliničko odlučivanje; prekidi rada; sigurnost bolesnika.

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Introduction

The emergency department (ED) is one of the most dynamic and demanding clinical environments within the healthcare system. Clinical work is performed under conditions of time pressure, unpredictable patient inflow, varying levels of illness severity, and the need for rapid decision-making (1). In this setting, healthcare professionals simultaneously assess patients, prioritize care, perform diagnostic and therapeutic interventions, communicate with team members, and document clinical activities (2). Such complexity requires a high level of concentration, rapid information processing, and the ability to manage multiple tasks concurrently (1,3).

The development of digital technologies has substantially transformed workflow organization in emergency medicine. Electronic health records, continuous patient monitoring systems, laboratory and radiology information systems, and various digital communication platforms enable faster access to clinical data, improved coordination of care, and greater availability of real-time information (4). These advances have the potential to facilitate timely clinical decision-making and improve patient outcomes. However, alongside these advantages, digitalization has introduced new demands that may increase the cognitive burden on healthcare professionals, particularly in environments where decisions must be made under significant time pressure (5).

Digital cognitive overload occurs when the volume of information, concurrent tasks, and interruptions exceeds clinicians' capacity to efficiently process information and make safe decisions.

In routine clinical practice, healthcare professionals in the ED are frequently required to simultaneously process information from multiple sources. These include continuous monitoring of vital signs, electronic documentation, interpretation of laboratory and radiological findings, communication with team members, and responses to alarms and other notifications (6). In addition, workflow is often interrupted by telephone calls, requests for consultation, or the arrival of new patients. When these demands occur continuously and overlap, they place increasing strain on attention and working memory, potentially compromising the quality of clinical decision-making (1,5).

Within this context, the concept of digital cognitive overload has gained increasing attention. It refers to a state in which the volume of information, the number of concurrent tasks, and the frequency of workflow interruptions exceed an individual's capacity to efficiently process and integrate information for decision-making (3). Importantly, digital cognitive overload represents more than a subjective perception of mental fatigue; it is associated with measurable reductions in information-processing efficiency, an increased risk of errors, and impaired ability to sustain attention.

The consequences of excessive cognitive load are particularly pronounced in the emergency department. Even brief lapses in attention may result in delayed recognition of patient deterioration, inaccurate prioritization, or failures in communication within the clinical team (2). These factors increase the risk of patient safety incidents, particularly in situations requiring rapid and precise coordination among multiple healthcare professionals. Furthermore, chronic exposure to excessive cognitive demands may contribute to mental fatigue, reduced work performance, and professional burnout (7).

The aim of this review is to examine the role of digital cognitive overload in the emergency department, with particular emphasis on its impact on clinical performance, decision-making, and patient safety. In addition, the review seeks to identify the principal sources of digital cognitive burden and to highlight potential strategies for reducing cognitive load and improving the alignment of digital systems with the needs of contemporary clinical practice.

Methodology

This study was designed as a narrative review of recent scientific and professional literature with the aim of synthesizing current knowledge on digital cognitive overload in the emergency department. A narrative review approach was selected because it allows the integration of heterogeneous sources, including studies from emergency medicine, nursing, health informatics, ergonomics, and human factors, which provide complementary perspectives on this topic.

The literature search was conducted using the PubMed, Scopus, and Web of Science databases. Publications from 2015 onwards were considered, with particular emphasis on recent studies reflecting contemporary trends in healthcare digitalization. The search strategy included keywords related to cognitive workload, digital health systems, workflow interruptions, alarm systems, electronic health records, and patient safety in acute clinical settings.

The review included original research articles, systematic and narrative reviews, and relevant professional publications examining the impact of digital technologies on the work of healthcare professionals in emergency departments, intensive care units, and other acute care settings. Particular attention was given to studies investigating the relationship between cognitive workload, clinical performance, and patient safety outcomes.

Studies focusing exclusively on the technical development of software solutions without clinical application, investigations conducted in non-clinical settings, and publications without a clear relevance to clinical practice or patient safety were excluded. This approach ensured that the review included literature directly applicable to the emergency department setting.

Table 1. Main Sources of Digital Cognitive Overload in the Emergency Department

Source	Description	Consequence
Electronic medical records (6,8)	Multiple data entries and complex system navigation	Fragmentation of attention and prolonged information-processing time
Alarm systems and monitors (9,10,27)	Large number of auditory and visual alerts, often with low clinical relevance	Alarm fatigue and reduced sensitivity to important signals
Work interruptions (1,11,17,22,23)	Telephone calls, questions from team members, and arrival of new patients	Loss of focus and increased risk of errors
Parallel use of multiple systems (6,12,13)	Insufficient integration of laboratory, radiology, and documentation systems	Increased mental workload and impaired navigation
Continuous data interpretation (2,6,12)	Large volume of information requiring rapid assessment	Impaired decision-making and selective information processing

Source: Prepared by the author based on a synthesis of the literature (1–3,6,8–13,17,22,23,27).

This study did not involve human participants or the processing of personal data; therefore, ethics committee approval was not required.

Discussion

Sources of Digital Cognitive Overload in the Emergency Department

The cognitive demands of the digital environment in the emergency department arise from the combination of multiple interrelated factors that operate simultaneously and cumulatively burden healthcare professionals' attention and working memory (3). Rather than resulting from a single source, digital cognitive overload reflects the interaction of numerous technological, organizational, and human factors that collectively create substantial challenges in everyday clinical practice.

One of the principal contributors to digital cognitive overload is the electronic health record (EHR). Although EHR systems improve data standardization and accessibility, their use often requires repeated data entry, navigation through complex interfaces, and frequent switching between different modules (8). Workflows characterized by repetitive documentation, complex navigation, and continuous transitions between system interfaces may fragment attention and prolong the time required to process clinical information, particularly in situations that demand rapid decision-making.

Patient monitoring systems and clinical alarm systems represent another major source of cognitive burden. Patients in the ED are frequently connected to multiple monitoring devices that generate large numbers of audible and visual alerts (2,9). A high frequency of alarms, particularly those lacking clinical relevance, may contribute to alarm fatigue and reduce clinicians' ability to recognize alerts requiring immediate intervention (10). Consequently, an environment characterized by continuous auditory and visual stimuli requires constant redistribution of attention and increases mental workload.

Frequent workflow interruptions further intensify cognitive demands. In the emergency department, interruptions are an integral part of routine clinical practice and include telephone calls, questions from team members, the arrival of new patients, and additional documentation requests (11). Such interruptions increase the risk of clinical errors and reduce work efficiency.

The concurrent use of multiple digital systems further increases workflow complexity. Healthcare professionals often interact simultaneously with electronic documentation systems, laboratory information systems, radiology platforms, and digital communication tools (8,12). Insufficient interoperability between these systems may result in duplicated information, inefficient navigation, and increased cognitive workload. Rather than simplifying clinical practice, technology may, under such circumstances, become an additional source of complexity (12).

An important but often overlooked contributor to cognitive overload is the continuous need to interpret large volumes of clinical data. The increasing availability of patient information requires rapid assessment and integration into clinical decision-making (2). Under conditions of significant time pressure, these cognitive demands may exceed an individual's capacity for efficient information processing.

In addition to these technological and organizational factors, individual characteristics also play an important role. Professional experience, level of training, and the ability to manage attention all influence susceptibility to cognitive overload (13). Less experienced healthcare professionals may be particularly vulnerable because they require greater cognitive effort to process clinical information, whereas experienced clinicians, despite greater routine and expertise, may be exposed to chronic cognitive burden resulting from prolonged work in a highly demanding environment (14).

Digital cognitive overload in the emergency department results from the cumulative interaction of technological, organizational, and human factors rather than from a single source.

Overall, digital cognitive overload in the emergency department is not attributable to a single cause but rather reflects the complex interaction of technological, organizational, and human factors. Understanding these contributing factors represents an essential step toward developing strategies aimed at reducing cognitive burden and improving patient safety.

Impact of Digital Cognitive Overload on Clinical Performance

Excessive digital demands have a direct and measurable impact on the clinical performance of healthcare professionals working in the emergency department (ED). In an environment where decisions must be made rapidly and often on the basis of incomplete information, any disruption in information processing or sustained attention may have significant consequences for patient management (15).

One of the most important aspects of clinical performance affected by cognitive overload is decision-making. Under conditions of increased digital workload, working memory capacity is reduced and the integration of information from multiple sources becomes more difficult (2,13). As a result, healthcare professionals may make decisions based on incomplete or selectively processed information, increasing the risk of diagnostic errors and suboptimal therapeutic interventions (16). These challenges are particularly pronounced in the emergency department, where patients' clinical conditions may change rapidly. Furthermore, the complexity of digital systems and the need to use multiple platforms simultaneously may slow workflow, fragment attention, and reduce the overall efficiency of healthcare professionals (17).

Another critical component of clinical performance is the ability to maintain situational awareness (18). In the emergency department, situational awareness involves continuous monitoring of patient status, understanding the clinical context, and anticipating potential complications. The large volume of information and continuous stream of digital stimuli may compromise this ability by making it more difficult to distinguish clinically relevant information from less important data (12). Consequently, deterioration in a patient's condition may be recognized later, and early signs of complications may be overlooked.

Team communication is also highly susceptible to the effects of cognitive overload. Under conditions of increased mental workload, healthcare professionals may shorten or simplify communication, thereby increasing the risk of misunderstandings (19). Workflow interruptions and digital distractions further impair information exchange among team members, particularly during critical phases of patient care (20). Communication failures may directly affect care coordination and compromise patient safety.

Digital cognitive overload is also associated with increased mental fatigue, which develops following prolonged exposure to high information-processing demands. Mental fatigue reduces concentration, slows reaction time, and increases susceptibility to errors (21). In the emergency department, where sustained attention is essential, these effects may significantly compromise the quality of patient care.

The consequences of excessive cognitive workload often manifest as a gradual decline in performance over the course of a work shift (2). As cognitive demands accumulate, the ability to maintain a consistently high level of clinical performance progressively decreases, leading to an increased likelihood of errors, particularly during the later stages of the shift (22). Collectively, these factors adversely affect key components of clinical performance, including clinical decision-making, workflow efficiency, situational awareness, and communication within the healthcare team.

Impact of Digital Cognitive Overload on Patient Safety

Patient safety is a fundamental indicator of healthcare quality, particularly in the emergency department, where clinical decisions are made rapidly and often under conditions of considerable uncertainty (23). In such an environment, excessive digital cognitive workload is not merely an individual challenge for healthcare professionals but also a systemic risk that may directly affect patient safety outcomes.

One of the primary mechanisms through which cognitive overload compromises patient safety is by increasing the likelihood of clinical errors. Under conditions of excessive demands on attention and working memory, healthcare professionals may overlook critical information, misinterpret clinical findings, or make decisions based on incomplete data (22). Importantly, these errors are not necessarily the result of insufficient knowledge or experience but frequently reflect the limitations of human cognitive capacity under conditions of high workload.

Workflow interruptions and digital distractions represent another important threat to patient safety. Healthcare professionals in the ED are continuously exposed to multiple simultaneous stimuli, including monitor alarms, notifications from electronic information systems, and communication with other members of the clinical team (20). Each interruption increases the risk of losing focus and forgetting previously initiated tasks. During medication administration, clinical documentation, or patient monitoring, such interruptions may lead to delays in intervention or errors in task execution (17).

Digital cognitive overload is a systemic patient-safety risk that can delay recognition of clinical deterioration, increase errors, and impair communication and timely clinical responses.

Excessive digital demands may also impair the timeliness of clinical responses. When healthcare professionals must

Table 2. Strategies for Reducing Digital Cognitive Overload in the Emergency Department

Level	Strategy	Clinical effect
Technological	Simplification of user interfaces (29,30)	Reduced information-processing time
Technological	Filtering and prioritization of alarms (27,31)	Reduced distractions and alarm fatigue
Technological	Integration of digital systems (6,12,29)	Easier access to information and reduced mental workload
Organizational	Standardization of protocols (32)	Reduced need for continuous decision-making
Organizational	Clear distribution of responsibilities (32,33)	Improved coordination and patient safety
Organizational	Limiting interruptions during critical tasks (17,32,33)	Preservation of focus and reduction of errors
Individual	Education on cognitive workload (2,3,34)	Improved decision-making
Individual	Training in prioritization and time management (2,17)	Increased work efficiency
Individual	Simulation-based training (35)	Better preparation for high-workload situations

Source: Prepared by the author based on a synthesis of the literature (2,3,6,12,17,27,29–35).

simultaneously process large volumes of information, the time required to recognize clinically significant changes may be prolonged (22). Delayed recognition of patient deterioration may have serious consequences, particularly in acute conditions requiring immediate intervention (24).

Reliable communication within the healthcare team is another essential component of patient safety. Increased cognitive workload may lead to simplified or incomplete communication, thereby increasing the risk of misunderstandings (25). Ambiguous or insufficiently precise information exchange may result in misinterpretation of clinical instructions, delays in treatment, or duplication of interventions (26).

Although digital systems are designed to enhance patient safety, they may under certain circumstances introduce additional risks. The large number of electronic alerts and notifications may lead to reduced responsiveness to clinically important warnings, a phenomenon commonly referred to as alert fatigue (27). When healthcare professionals are exposed to excessive numbers of digital alerts, important notifications are more likely to be ignored or their response delayed.

The cumulative effects of prolonged cognitive workload become particularly evident during extended work shifts. As mental fatigue increases, the ability to maintain sustained attention and accuracy progressively declines, further increasing the likelihood of errors (28). Consequently, even routine and standardized clinical tasks may be performed with greater variability and a higher risk of safety incidents.

Patient safety incidents rarely result from a single contributing factor. Instead, they typically arise from the interaction of multiple elements, including organizational processes, technological systems, and human factors. Digital cognitive overload acts as an intermediary mechanism that amplifies the effects of these risks and reduces healthcare professionals' ability to respond promptly to changes in the clinical environment (17,22).

Overall, digital cognitive overload represents a significant but still underrecognized risk factor for patient safety in the emergency department. A better understanding of its effects is essential for developing effective strategies aimed at reducing clinical errors, improving working conditions, and enhancing the overall quality and safety of patient care.

Strategies to Reduce Digital Cognitive Overload in the Emergency Department

Reducing digital cognitive overload in the emergency department (ED) requires a systematic, multilevel approach that encompasses organizational changes, optimization of digital technologies, and the development of individual competencies among healthcare professionals (17). Because digital cognitive overload arises from the complex interaction between humans, technology, and the work environment, effective interventions must address all of these domains.

One of the key strategies involves optimizing digital systems. Clinical information systems should be designed to support, rather than burden, the work of healthcare professionals (8,29). This includes simplifying user interfaces, reducing unnecessary data entry steps, and presenting clinical information in accordance with users' priorities. Systems requiring repeated entry of identical information or presenting data in complex and poorly organized formats substantially increase cognitive workload and reduce work efficiency (30).

Particular attention should also be paid to the management of digital notifications and alarm systems. A large number of alerts, especially those of limited clinical relevance, may lead to alert fatigue and reduced responsiveness to important warnings (30). Prioritizing notifications, filtering non-essential alerts, and adjusting alarm thresholds according to the clinical context can substantially reduce unnecessary workflow interruptions (31). Such measures enable healthcare professionals to focus their attention on clinically relevant information and support more effective decision-making.

Work organization also plays an important role in reducing cognitive workload. Clearly defined team responsibilities, standardized clinical workflows, and structured protocols can reduce the need for repeated decision-making in routine situations (32). By minimizing routine cognitive demands, workflow interruptions, and the need to process multiple

information streams simultaneously, healthcare professionals can devote greater attention to clinically critical tasks, such as assessing unstable patients and making timely therapeutic decisions (33).

In the emergency department, where interruptions are frequent, specific organizational measures may further reduce distractions and the risk of errors. These include limiting non-urgent communication during critical procedures, establishing interruption-free zones during medication administration, and using visual indicators to signal that high-risk tasks are being performed.

Reducing digital cognitive overload requires a multilevel approach that combines better-designed digital systems, smarter alarm management, optimized workflows, and targeted staff education

Education of healthcare professionals represents another essential component of reducing cognitive overload. Understanding the concept of cognitive workload and its effects on clinical performance may help clinicians recognize high-risk situations and adapt their work practices accordingly (34). Educational initiatives may include training in time management, task prioritization, and effective team communication. In this context, simulation-based training may be particularly valuable, as it enables healthcare professionals to practice working under conditions of high cognitive demand without compromising patient safety (35).

The role of nurses in mitigating cognitive overload is particularly important. As healthcare professionals who remain continuously present at the patient's bedside, nurses play a central role in workflow organization, prioritization of care, and coordination of clinical activities. Their experience and ability to identify clinically relevant information in complex environments constitute important protective factors for maintaining patient safety (2,17). Furthermore, actively involving nurses in the design and adaptation of digital systems may contribute to the development of solutions that are better aligned with the realities of clinical practice (34).

Technological innovations may also contribute to reducing cognitive workload, provided they are implemented appropriately (17). Automation of routine tasks, integration of multiple information systems, and the use of intelligent clinical decision support systems may reduce the need for manual data entry and facilitate rapid access to relevant clinical information (6). However, it is essential to ensure that these technologies do not introduce additional cognitive burden through unnecessarily complex or non-transparent functionalities.

At the organizational level, it is important to recognize cognitive workload associated with digital systems as a significant occupational challenge (2). Systematic assessment of cognitive workload, analysis of clinical workflows, and active involvement of healthcare professionals in decisions regarding the implementation of new technologies may contribute to creating a safer and more efficient work environment. Measures promoting adequate rest, task rotation, and balanced work schedules may further reduce the cumulative effects of cognitive overload during clinical shifts (36).

Healthcare professionals should be actively involved in the design and implementation of digital systems to ensure that technology supports clinical work rather than adding to cognitive burden.

The overarching goal of these strategies is to achieve an appropriate balance between technological capabilities and human cognitive capacity. Only an integrated approach that acknowledges the complexity of emergency department practice can effectively reduce digital cognitive overload and improve patient safety.

Conclusion

Digital cognitive overload represents an increasingly important, yet still underrecognized, challenge in everyday emergency department (ED) practice. In an environment characterized by time pressure, unpredictability, and the need to manage multiple concurrent tasks, continuous exposure to digital information, notifications, and workflow interruptions may exceed the cognitive capacity of healthcare professionals. Consequently, the risk of clinical errors, delayed responses, and communication failures increases, directly affecting patient safety.

Current evidence suggests that excessive digital demands are not solely a consequence of the growing use of technology, but rather of the way digital systems are integrated into clinical workflows. Systems that are not aligned with the practical needs of emergency care may increase workflow complexity and impair clinical decision-making. Conversely, well-designed and optimized digital tools have the potential to improve workflow efficiency, support clinical decision-making, and enhance the quality and safety of patient care.

Reducing the cognitive demands imposed by digital systems requires coordinated interventions at multiple levels, including optimization of digital technologies, improvements in workflow organization, and continuous education of healthcare professionals. Nurses play a particularly important role in this process, as their continuous presence at the patient's bedside and responsibility for coordinating clinical activities contribute substantially to maintaining patient safety in a complex healthcare environment.

Ultimately, recognizing and proactively addressing digital cognitive overload represents an important step toward improving patient safety and the overall quality of emergency care. Future research should further elucidate the mechanisms underlying digital cognitive overload and evaluate the effectiveness of targeted interventions aimed at reducing cognitive burden and optimizing digital workflows in clinical practice.

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ORIGINAL ARTICLE / IZVORNI ZNANSTVENI ČLANAK

IS HEAD CT ALWAYS NECESSARY? EXPERIENCES WITH THE CANADIAN HEAD CT RULE IN THE EMERGENCY DEPARTMENT SETTING

JE LI CT GLAVE UVIJEK POTREBAN? ISKUSTVA S PRIMJENOM KANADSKOG PRAVILA ZA CT GLAVE U HITNOM BOLNIČKOM PRIJAMU

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Abstract

Introduction: Head injuries are among the most common reasons for patient presentation to the Emergency Department and represent a significant diagnostic challenge. Computed tomography (CT) is considered the gold standard in the initial assessment of patients with head trauma due to its availability and high sensitivity in detecting intracranial injuries. However, the widespread and often indiscriminate use of CT contributes to emergency department overcrowding and prolonged patient length of stay. In an effort to rationalize CT utilization, several clinical decision-making tools have been developed, among which the Canadian Head CT Rule (CCHR) holds a prominent role. The aim of this retrospective study was to evaluate the use of the Canadian Head CT Rule (CCHR) in patients presenting to the Emergency Department and to assess its potential in rationalizing indications for head CT without compromising patient safety.

Materials and methods: This retrospective observational study analyzed patients admitted with head injuries over a one-year period, with data collected from medical records. The results were analyzed using descriptive statistical methods and presented as absolute and relative values.

Results: The study sample included 272 patients with head injuries who underwent head CT in the Emergency Department. Based on the presence of exclusion criteria for the application of the Canadian Head CT Rule (CCHR), 54 patients were excluded from the study, resulting in a final sample size of 218 patients. Exclusion criteria included age under 16 years, anticoagulant therapy, and seizure occurring immediately after the injury. Of the total sample, 65% were male and 35% female. The most common positive finding within the CCHR criteria was amnesia lasting longer than 30 minutes, present in 81 patients, whereas signs of skull or basilar skull fracture were the least common, observed in only 5 patients. In 70% of performed head CT scans, there was an indication for imaging according to the CCHR criteria. In the remaining 30% of cases, CT imaging was not indicated according to the CCHR. Overall, CT findings were normal in 82% of patients, while 18% had pathological findings. Among patients with normal CT findings, an indication for CT according to the CCHR was present in 89% of cases. Among patients with pathological CT findings, the CCHR did not indicate CT imaging in 11 % of cases.

Conclusion: This analysis demonstrates that the CCHR has high sensitivity but limited specificity. The large number of normal CT findings despite fulfilled criteria suggests potential overutilization of imaging. On the other hand, the substantial proportion of pathological CT findings in patients for whom the CCHR did not indicate CT confirms

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that the rule should not be applied in isolation. The CCHR is a valuable decision-making tool, but it should always be combined with thorough clinical assessment.

Keywords: computed tomography; emergency medicine; head trauma

Sažetak

Uvod: Ozljede glave jedan su od najčešćih razloga dolaska pacijenata u Centar urgentne medicine te predstavljaju značajan dijagnostički izazov. Kompjuterizirana tomografija (CT) predstavlja zlatni standard u inicijalnoj dijagnostici pacijenta s traumom glave zbog svoje dostupnosti i visoke osjetljivosti u detekciji intrakranijalnih ozljeda. Međutim, široka i često nekritična primjena CT-a dovodi do prevelikog opterećenja hitnih službi te produženog boravka pacijenata u urgentnom centru. S ciljem racionalizacije uporabe CT-a razvijeni su klinički alati za donošenje odluka, među kojima Canadian Head CT Rule (CCHR) zauzima istaknuto mjesto. Cilj ove retrospektivne studije bio je analizirati uporabu CCHT skora kod pacijenata u Centru urgentne medicine, te procijeniti njegov potencijal u racionalizaciji indikacija za CT glave bez ugrožavanja sigurnosti pacijenta.

Materijali i metode: Riječ je o retrospektivnoj opservacijskoj studiji kojom su analizirani pacijenti zaprimljeni zbog ozljede glave u toku jedne godine, a podaci su prikupljeni na osnovu medicinske dokumentacije. Rezultati su analizirani deskriptivnim statističkim metodama te prikazani u obliku apsolutnih i relativnih vrijednosti

Rezultati: Ukupni uzorak je obuhvatio 272 pacijenata sa ozljedom glave kojima je urađen CT glave u urgentnom centru. Na osnovu prisustva isključujućih kriterija za primjenu Canadian CT head rule CCHR) operacione skale iz istraživanja su isključena 54 ispitanika, te ukupan uzorak za ovo istraživanje iznosi 218. Isključujući kriteriji su životna dob ispod 16 godina, uzimanje antikoagulanasa i epi-napad neposredno nakon ozljede. Od ukupnog uzorka, 65 % su činili muškarci, a 35 % žene. Najčešći pozitivan odgovor u CCHR skoru kod naših pacijenata bilo je prisustvo amnezije za period duži od 30 minuta koji je bio prisutan kod 81 pacijenta, dok je najrijeđe prisutan bio znak preloma lobanja/baze lobanje – u svega 5 pacijenta. Kod 70 % učinjenih CT snimanja zbog ozljede glave, postojala je indikacija po CCHR skoru. U prostalih 30 % CT snimanje nije bilo indicirano po CCHR skoru. U ukupno 82 % pacijenata CT nalaz je bio uredan, dok je u 18% CT nalaz bio patološki. Kod pacijenata koji su imali uredan CT nalaz, u 89 % slučajeva je postojala indikacija za CT snimanjem. Među pacijentima koji su imali patoški nalaz CT-a, u 11 % slučajeva CCHR skor nije indicirao CT.

Zaključak: Ova analiza pokazuje da CCHR ima visoku osjetljivost, ali ograničenu specifičnost. Veliki broj urednih CT nalaza unatoč ispunjenim kriterijima ukazuje na moguću prekomjernu uporabu snimanja. S druge strane, zabilježen je visok procent patoloških nalaza kod kojih CCHR nije indicirao CT što potvrđuje da pravilno ne smije biti primjenjeno izolirano. CCHR je vrijedan alat u donošenju odluka, ali ga je potrebno kombinirati s kliničkom procjenom.

Ključne riječi: hitna medicina; kompjuterizirana tomografija; trauma glave

Introduction

Head injuries represent one of the most common reasons for visits to emergency services and emergency departments worldwide. In general, head injuries are among the most frequent types of both open and closed traumatic injuries in humans. They are also encountered across all age groups. It is important to emphasize that the pathophysiology, initial diagnostic approach, and management of head injuries differ significantly among different age populations (1). Regardless of these differences, computed tomography (CT) remains the gold standard for the diagnosis of head injuries (2). Although CT is therefore an indispensable diagnostic tool in emergency departments and acute care settings, the justification for its widespread use continues to be questioned. To some extent, owing to its broad availability and ease of application, CT has become a form of triage method in the urgent diagnostic evaluation of traumatic injuries. Consequently, numerous clinical decision-making tools have been developed to guide diagnostic assessment. Several diagnostic scoring systems and algorithms have been designed to identify patients who genuinely require CT imaging, while simultaneously reducing unnecessary CT utilization without compromising patient safety.

The Canadian Head CT Rule (CCHR) is currently one of the most commonly cited and widely used clinical decision tools in emergency medicine settings (3). The CCHR was developed

at the Ottawa Hospital Research Institute and is intended to facilitate the identification of patients at increased risk of clinically significant traumatic brain injury among individuals presenting with head trauma. Compared with previously developed algorithms, such as the New Orleans Criteria, the CCHR has demonstrated higher specificity, which is why it is considered one of the most broadly applicable diagnostic tools in cases of minor head injury (4).

Head injuries represent one of the most common reasons for patient presentation to Emergency Departments.

It is important to note that the CCHR is structured as a clinical assessment tool consisting of 10 questions, with the first three representing the so-called "exclusion criteria." These exclusion criteria include patients younger than 16 years of age at the time of injury, patients receiving chronic anticoagulant therapy, and patients who experienced a post-traumatic seizure immediately following the head injury. The presence of one or more of these factors renders the CCHR inapplicable in the specific clinical case, and its use in such patients is therefore not recommended. In these populations, serious traumatic brain injury cannot be reliably identified using the CCHR. Furthermore, the CCHR is intended for patients with clinically minor head injuries. It is not designed for use in polytraumatized patients or in patients with severe traumatic brain injury.

The aim of this study was to evaluate whether implementation of the CCHR in patients presenting to our Emergency Department could reduce the use of head CT for diagnostic purposes without compromising patient safety.

Although computed tomography (CT) is widely available, it is frequently overutilized in the evaluation of head trauma, often without a clear clinical indication.

Materials and methods

This retrospective observational study analyzed all patients presenting with minor head injury to the Emergency Department of Cantonal Hospital Bihać over a one-year period. It is important to emphasize that the Canadian Head CT Rule (CCHR) was not applied prior to patient admission or before the decision to perform CT imaging. Instead, the CCHR was applied retrospectively, meaning that the CCHR score was calculated for all patients who had already been examined, treated, and underwent head CT imaging due to head trauma.

Data were obtained through review of medical records and the hospital information system. Personal patient data and patient initials were not used in the study. The use of medical documentation was approved by the institutional director through an internal administrative authorization. The results were statistically analyzed and presented in the form of tables, graphs, and descriptive text.

Results

The total number of patients admitted to the Emergency Department of our hospital due to head trauma was 272. This number represents patients who underwent computed tomography (CT) imaging of the head following the initial clinical assessment and examination for head injury. During the retrospective application of the Canadian CT Head Rule (CCHR), exclusion criteria were taken into consideration. Accordingly, the CCHR could not be applied to 54 patients, as these included individuals younger than 16 years of age, patients receiving long-term anticoagulant therapy, and patients who experienced a seizure immediately following head trauma. Consequently, the total number of cases eligible for CCHR score calculation was 218.

Regarding sex distribution, male patients predominated, accounting for 65% of the study population, while female patients comprised 35%. Following the application of the CCHR in patients who underwent head CT imaging, the frequency of individual parameters considered by the CCHR when determining recommendations for CT imaging was analyzed. The most frequently positive variable among our patients was retrograde amnesia lasting longer than 30 minutes prior to injury, which was identified in 37.2% of cases. Other parameters were observed less frequently, with suspected open or depressed skull fracture being the least common criterion, present in only 2.3% of cases.

Within our study sample, at least one positive CCHR criterion was identified in 71% of patients following application of the score, whereas no positive CCHR criteria were present in 29% of patients. Considering the methodology and recommendations of the CCHR, head CT imaging was indicated in 70% of patients, while no indication for CT imaging was present in 30% of cases.

Although all patients underwent head CT imaging, normal CT findings were reported in 82% of patients. Pathological CT findings, indicating the presence of intracranial injuries, were identified in 18% of cases. Analysis of patients with normal CT findings demonstrated that, following application of the CCHR, CT imaging had not been indicated in 89.2% of cases. Conversely, among patients with pathological CT findings, retrospective application of the CCHR demonstrated that head CT imaging would not have been indicated in 10.8% of patients.

Detailed results are summarized in Table 1.

Discussion

Analysis of the results obtained in our study clearly demonstrated that patients with head injuries were predominantly younger males. This finding is consistent with

Table 1. Patient demographics overview

Sociodemographic characteristics	Age		50,47±21,63 (16-89)
	Gender	Male	141 (64,7%)
		Female	77 (35,3%)
CCHR criteria	Age >65 years	No	152 (69,7)
		Yes	66 (30,3)
	GCS		14,79±1,08 (3-15)
	GCS <15	No	203 (93,1%)
		Yes	15 (6,9%)
	Vomiting >2 puta	No	178 (81,7%)
		Yes	40 (18,3%)
	Retrograde amnesia >30 min.	No	137 (62,8%)
		Yes	81 (37,2%)
	Dangerous injury mechanism	No	187 (85,8%)
		Yes	31 (14,2%)
	Signs of skull fracture or basilar skull fracture	No	213 (87,7%)
		Yes	5 (2,3%)
	At least one of CCHR criteria is met	No	62 (28,4%)
		Yes	156 (71,6%)
According to CCHR Head CT was indicated		Head CT was not indicated	65 (29,8%)
		153 (70,2%)	
CT results		Normal CT	178 (81,7%)
Pathological CT		40 (18,3%)	

recent international studies confirming that males are more frequently affected by head trauma.(5)

Taking into account the exclusion criteria that render the Canadian CT Head Rule (CCHR) inapplicable in specific cases of head injury, the total number of patients who underwent head computed tomography (CT) imaging in our Emergency Department was 272. Since the CCHR was applied retrospectively to patients who had already undergone clinical evaluation and head CT imaging, we were able to exclude patients receiving anticoagulant therapy, patients younger than 16 years of age, and patients who experienced seizures immediately following the injury. As there were 54 such patients, the final sample on which the CCHR was retrospectively applied consisted of 218 patients.

It is important to emphasize that, in our Emergency Department, head CT imaging is indicated only in patients whose clinical presentation raises suspicion of significant traumatic brain injury. Patients with very mild head trauma are generally not referred for CT imaging. Considering that head injuries are globally among the most common reasons for Emergency Department visits (6), the findings of our analysis are consistent with the expected prevalence of traumatic head injuries.

We demonstrated that the CCHR is a highly sensitive clinical decision-making tool, with CT imaging indicated in more than two-thirds of our cases.

Following the analysis of sociodemographic characteristics, the CCHR was retrospectively applied to each individual case in order to assess whether the rule would inaccurately classify patients or accurately identify those requiring CT imaging of the head. It should be emphasized that the CCHR is structured as a clinical decision-making tool in which the presence or absence of specific symptoms in patients with minor head injury is evaluated, after which recommendations regarding CT imaging are generated based on the recorded findings. Analysis of symptoms in our study population demonstrated that the most common positive CCHR criterion was the presence of retrograde amnesia lasting longer than 30 minutes prior to the traumatic event, which was observed in 37.2% of patients. In clinical practice, this symptom was most commonly identified through the patient's inability to reconstruct the events preceding the injury, which was interpreted as retrograde amnesia. The duration of retrograde amnesia has been shown in most studies to correlate with the severity of brain injury (7), thereby justifying the use of head CT imaging in such patients.

However, in nearly 11% of cases, the CCHR would not have recommended CT imaging despite the presence of findings revealing significant intracranial injury.

The second most frequent positive CCHR criterion in our sample was age greater than 65 years. Previous studies have clearly demonstrated that elderly patients are at increased risk of more severe intracranial injury; therefore, the CCHR appropriately recommends CT imaging in this patient population. (8) As illustrated graphically, the least frequently encountered CCHR criterion in our cohort was suspicion of an open or depressed skull fracture.

Subsequently, we analyzed the number of patients for whom the CCHR, based on the previously entered criteria, would recommend CT imaging of the brain. It is important to reiterate that all patients included in our sample had already undergone head CT imaging, while the primary objective of the study was to evaluate the potential of the CCHR to safely reduce the number of unnecessary CT examinations. In our cohort, the CCHR would have recommended CT imaging in 70% of cases, whereas CT imaging would not have been indicated in 30% of patients. Based solely on this finding, it could be argued that CT imaging may have been unnecessary in approximately 30% of cases. However, it is evident that the CCHR cannot be used as a triage tool. Previous studies have demonstrated its effectiveness only when interpreted in conjunction with clinical findings. (9)

We then analyzed head CT findings in our patient cohort. It should be clarified that CT findings without evidence of traumatic pathology were classified as normal CT findings, whereas pathological CT findings were defined as those demonstrating any form of traumatic injury involving the skull and/or brain. Normal CT findings were observed in 82% of patients, while pathological findings were present in 18% of cases. The proportion of CT scans demonstrating traumatic pathology correlates with findings from studies with larger patient samples (10) and therefore cannot be interpreted as evidence of unnecessary or indiscriminate CT utilization in patients with head trauma.

Perhaps the most important aspect of the study was the evaluation of the ability of the CCHR to identify patients with intracranial pathology. Among patients with normal CT findings, the CCHR would nevertheless have recommended CT imaging in 78% of cases. However, among patients whose CT findings demonstrated some form of intracranial injury, application of the CCHR alone would not have indicated CT imaging in 10.8% of cases. This finding suggests that these cases would potentially have been missed.

This result strongly emphasizes that the CCHR should be regarded as a clinical decision-support tool rather than a screening method and, as such, should not be used independently or in isolation from comprehensive clinical assessment that considers the broader clinical context of the patient. Therefore, while the CCHR demonstrates potential in reducing the number of unnecessary CT examinations in patients with mild head injury, it also has limitations regarding its specificity. (11)

Conclusion

Based on the results of our study, it can be concluded that head injuries, as one of the most common reasons for Emergency Department visits, represent a significant diagnostic challenge. Although head CT remains the gold standard in the evaluation of head trauma, its use is often non-selective.

The Canadian CT Head Rule (CCHR) is a highly sensitive clinical decision-making tool whose application may contribute to reducing the number of unnecessary head CT examinations. However, the CCHR is not a triage method and should not be applied in isolation, as a substantial proportion of pathological CT findings could otherwise remain undetected.

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