# IPERTENSIONE NEL SUD DELLA SVIZZERA - PREVALENZA E EFFICACIA DELLA PRESA IN CARICO

Francesca Cinieri, Martina Zandonà, Sebastien Sare, Franco Muggli, Rosaria Del Giorno, Luca Gabutti

Ricevuto: 24 marzo 2025,
revisionato: 18 aprile 2025,
accettato: 29 aprile 2025



ISSN print: 1421-1009
ISSN online: 3042-6138

DOI: 10.63648/zj52tm66

**Riassunto**

L'ipertensione, contribuendo in modo significativo alla morbilità e alla mortalità cardiovascolare, è una delle principali sfide per la salute pubblica a livello globale. Questo studio di popolazione ne analizza la prevalenza, la gestione medicamentosa e la sua efficacia nel cantone Ticino in Svizzera. Un totale di 1.202 individui ha partecipato allo studio, sottoponendosi a misurazioni della pressione arteriosa in ambulatorio e a monitoraggio pressorio delle 24 ore.

I risultati indicano che oltre il 40% della popolazione esaminata presentava livelli di pressione arteriosa ipertensivi secondo le linee guida ESC 2024 e ESH 2023. Un risultato chiave è che un individuo su quattro con ipertensione in ambulatorio aveva un'ipertensione da camice bianco, evidenziando l'importanza dell'ABPM per distinguere le elevazioni contestuali dei parametri pressori dall'ipertensione sostenuta. Inoltre, tre quarti dei soggetti diagnosticati con ipertensione in ambulatorio presentavano un'ipertensione di Grado 1, sottolineando la necessità di un intervento precoce attraverso modifiche dello stile di vita e trattamenti farmacologici, se necessario.

Preoccupante è la quota significativa di individui ipertesi che non ricevevano un trattamento adeguato. Tra i pazienti ipertesi, il 74% non era trattato e, tra coloro in terapia, l'80% non raggiungeva i livelli target di pressione arteriosa. Lo studio ha rilevato che l'85% dei pazienti in monoterapia rimaneva iperteso, indicando la possibile necessità di una terapia combinata e di un'ottimizzazione del trattamento.

Questi risultati evidenziano il ruolo essenziale dei medici di base nella diagnosi e nella gestione efficace dell'ipertensione. È infatti loro il compito di garantire una valutazione accurata della pressione arteriosa, promuovere cambiamenti dello stile di vita e adattare le terapie farmacologiche alle esigenze individuali. Un approccio globale e multifattoriale, che includa l'educazione del paziente, il monitoraggio regolare e strategie terapeutiche basate sull'evidenza, è cruciale per migliorare il controllo dell'ipertensione e ridurre i rischi cardiovascolari associati. Questo studio sottolinea l'urgente necessità di strategie di salute pubblica più efficaci per affrontare l'ipertensione e le sue conseguenze a lungo termine.

**Introduction**

Hypertension is a widespread condition with profound implications for global health. Often asymptomatic, it is referred to as the "silent killer," affecting 1.3 billion adults worldwide [1, 2]. Characterized by persistently elevated blood pressure (≥140/90 mmHg) [1, 2], hypertension is a leading cause of severe health complications such as heart disease, stroke, and kidney failure [3]. Despite its substantial health burden, hypertension frequently goes undiagnosed and inadequately managed, with only 21% of affected individuals achieving effective blood pressure control [1-3].

The economic impact of hypertension is equally significant. Uncontrolled blood pressure imposes substantial costs on healthcare infrastructures, particularly in treating complications such as heart diseases and strokes [3]. Individuals and families, particularly in low- and middle-income countries (LMICs), disproportionately bear these costs due to limited access to healthcare and essential medications [4].

Even in high-income countries, hypertension remains a pressing healthcare challenge due to its subtle onset and chronic progression, which demands consistent management and monitoring. In Switzerland, approximately 1.5 million adults aged 30–79 years are living with hypertension, which accounts for nearly one in three adults in this age group [5]. Addressing this issue is crucial, as achieving a 50% blood pressure control rate in Switzerland would require effective treatment for an additional 180,000 individuals, potentially preventing 18,000 deaths by 2040 [5].

National health studies, such as the May Measurement Month campaigns [6], have identified significant gaps in hypertension awareness and management in Switzerland. On one hand the survey confirmed that about one-third of the Swiss population has blood pressure values in the hypertensive domain, and on the other that only half of those diagnosed with hypertension had their blood pressure under control [7]. This also aligns with findings from the Swiss Health Survey [11], which reported that 19.5% of the population aged 15+ had high blood pressure in 2022, up from 14.7% in 2002. These trends underscore the growing prevalence of hypertension and highlight the importance of early interventions and

A cura dell'Istituto
di medicina
di famiglia USI

long-term strategies to address risk factors and prevent complications [6-8].
A specific management challenge is white coat hypertension (WCH), defined as elevated blood pressure readings (≥140/90 mmHg) observed only in clinical settings, with normal home or ambulatory measurements. Previously considered benign, WCH is now recognized as predictive of sustained hypertension and increased cardiovascular risk [9]. Additionally, natural fluctuations in blood pressure, such as a typical 10–20% nocturnal "dip," are important prognostic factors. The absence of this dipping pattern is associated with increased cardiovascular risk, including heart attacks, strokes, and kidney disease [10].
Current ESC and ESH guidelines recommend a multifaceted approach, combining lifestyle interventions—including dietary modifications, increased physical activity, and smoking cessation—with pharmacological therapies. Standard pharmacological interventions typically involve ACE inhibitors, angiotensin II receptor blockers, dihydropyridine calcium channel blockers, diuretics (thiazides and thiazide-like diuretics such as hydrochlorothiazide, chlorthalidone, and indapamide), and beta-blockers.
A recent Swiss study examining trends in potentially avoidable hospitalizations (PAH) due to hypertension (1998–2018) found that hypertension-related PAH patients were more likely younger, female, non-Swiss nationals, and admitted as emergencies, resulting in healthcare expenditures of approximately CHF 16.5 million in 2018 alone. This highlights the substantial economic impact of uncontrolled hypertension and underscores the need for enhanced prevention and management strategies [11].
Lifestyle factors significantly influence hypertension prevalence in Switzerland. The SAPALDIA cohort study identified obesity and physical inactivity as major contributors [12]. Furthermore, regional differences in hypertension awareness, treatment, and control exist, with urban areas generally performing better than rural regions. Linguistic disparities also affect management; Italian- and French-speaking regions exhibit lower awareness and treatment rates compared to the German-speaking region, influenced by factors such as healthcare access and cultural perceptions [13].
Unfortunately, data specific to hypertension in the Italian-speaking region of Switzerland remain limited. To address this gap, our study aims to characterize hypertension prevalence, management, and treatment outcomes in this region, providing valuable insights into locally relevant factors.

## Methods

This study is based on the Ticino Epidemiological Stiffness Study (TEST study), a cross-sectional population study conducted in the Canton of Ticino (Southern Switzerland) between 2017 and 2018. It involved residents aged 18 years and older which were recruited through random sampling from a mailing list provided by the Swiss Federal Statistical Department [18]. The TEST study adhered to the principles of the Helsinki Declaration of 1964 and was approved by the local Swiss ethics committee (CE 3115-2016-01718). All participants provided informed consent to take part in the study.
The study included a total of 1,202 participants. Each participant completed a standardized questionnaire designed to assess health status, medical history, dietary habits, and physical activity. Each subject was asked if he or she was aware of his/her values of blood pressure and whether he or she was taking antihypertensive drugs and in that case which ones. Blood samples were collected to analyze serum glucose, HbA1c, creatinine, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, total cholesterol, and cystatin. Additionally, a 24-hour urine collection was conducted, divided into "daytime" and "nighttime" periods based on the participants' self-reported sleep and wake times.
Regarding blood pressure, it was measured two times during the clinical visit and then each participant was equipped with an Ambulatory Blood Pressure Monitor (ABPM) for continuous 24-hour monitoring. The device recorded measurements every 30 minutes during the day and once per hour at night. Blood pressure monitoring was conducted on working days, and participants were instructed to follow their usual daily routine [15].
For the purposes of this study, in order to identify subjects with hypertension, we used the 2024 ESC and 2023 ESH guideline definitions: an office systolic blood pressure (BP) of ≥140 mmHg and/or diastolic BP of ≥90 mmHg or a systolic daytime ABPM ≥ 135 mmHg and/or nighttime ABPM ≥ 120 mmHg or a systolic 24h ABPM ≥ 130 mmHg and/or diastolic ≥ 80 mmHg. Stress-induced hypertension (also known as white-coat HT), was defined as elevated office blood pressure with normal ABPM measurements, while masked hypertension was defined as BP below the HT diagnostic threshold in office but above the HT diagnostic threshold in ABPM measurements. Blood pressure dipping was considered normal if the difference between daytime and nighttime systolic pressure was ≥10%.

## Results

A total of 1,202 subjects were included in the study, of whom 556

| | Total hypertensive subjects | Systolic blood pressure in office ≥140 mmHg | Diastolic blood pressure in office ≥90 mmHg | 24-hour systolic blood pressure ≥130 mmHg | 24-hour diastolic blood pressure ≥80 mmHg | Daytime systolic blood pressure ≥135 mmHg | Nighttime systolic blood pressure ≥120 mmHg |
|---|---|---|---|---|---|---|---|
| Number of subjects | 556 | 251 | 239 | 197 | 298 | 170 | 261 |
| % of the total | 46% | 21% | 20% | 16% | 25% | 14% | 22% |

**Tab. 1:** Main findings in the population.

(46%) were classified as hypertensive based on their levels of BP in office or at ABPM, or the presence of ongoing antihypertensive treatment.

Office blood pressure measurements indicated that 251 participants (21%) had systolic hypertension (≥140 mmHg), while 239 (20%) had diastolic hypertension (≥90 mmHg). Ambulatory blood pressure monitoring (ABPM) revealed that 197 individuals (16%) had 24-hour systolic hypertension (≥130 mmHg), whereas 298 (25%) presented with 24-hour diastolic hypertension (≥80 mmHg). Daytime systolic hypertension (≥135 mmHg) was detected in 170 subjects (14%), while nighttime systolic hypertension (≥120 mmHg) was observed in 261 subjects (22%). Among all subjects, 145 (26%) were undergoing antihypertensive therapy (**Table 1**).

Regarding office hypertension, 334 individuals exhibited elevated blood pressure in the clinical setting.

Stress-induced hypertension (also known as white-coat HT), defined as elevated office blood pressure with normal ABPM measurements, was identified in 88 subjects, representing 26% of those with office hypertension. Among the individuals with normal office blood pressure, 23% were diagnosed with masked hypertension, defined as BP below the HT diagnostic threshold in office but above the HT diagnostic threshold in ABPM measurements. The prevalence of non-dippers (difference between systolic daytime pressure and systolic nighttime pressure < 10%) was 55%.

Office blood pressure severity classification indicated that 242 participants (72% of those with office hypertension) had Grade 1 hypertension (systolic 140–159 mmHg and/or diastolic 90–99 mmHg). Grade 2 hypertension was observed in 77 subjects (23%) with values of systolic BP between 160 and 179 mmHg and/or diastolic between 100 and 109 mmHg, while Grade 3 hypertension (≥180/110 mmHg) was identified in 15 subjects (5%).

As far as the prevalence and treatment rates across different age groups, among younger individuals (18-40 years), 26% had HT, but only 1.4% of them were receiving treatment. In contrast, HT prevalence rises with age (47% in 41-65 years and 74% in >65 years), with a higher proportion of treated individuals in older groups, respectively 9.8% and 36% (**Fig. 1**).

Among hypertensive patients, 411 (74%) were not receiving any pharmacological treatment. Among the 145 treated individuals, 116 (80%) did not achieve target blood pressure levels. Specifically, among those on monotherapy (n=74), 63 remained hypertensive, representing 85% of this subgroup. Their mean office blood pressure was 139/88 mmHg, with a 24-hour average of 128/78 mmHg, daytime systolic blood pressure of 131 mmHg, and nighttime systolic blood pressure of 119 mmHg. Among patients on dual therapy (n=52), 39 remained hypertensive (75%), with an office blood pressure of 141/85 mmHg, 24-hour average of 127/78 mmHg, daytime systolic blood pressure of 130 mmHg, and nighttime systolic blood pressure of 119 mmHg. Lastly, among those on three or more medications (n=19), 14 remained hypertensive (73%). Their mean office blood pressure was 137/84 mmHg, with a 24-hour average of 122/78 mmHg, daytime systolic blood pres-

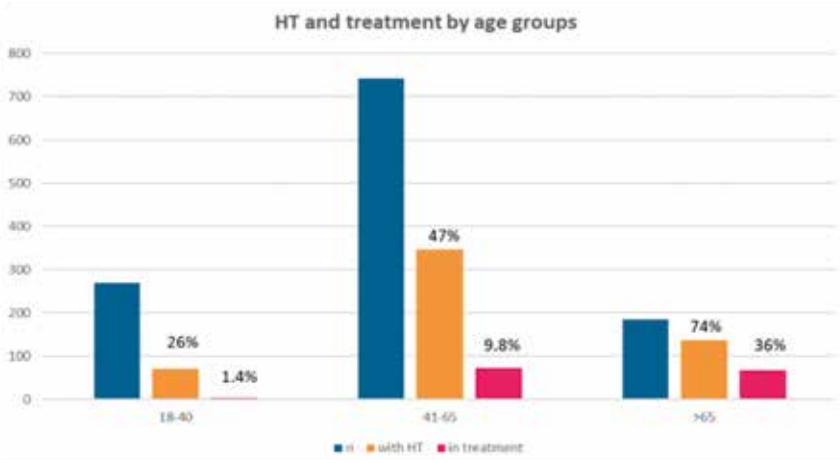


**Fig. 1:** Percentage of subjects with hypertension (orange) and treated with antihypertensive medications (pink) compared with total subjects (blue).

A cura dell'Istituto
di medicina
di famiglia USI

Università della Svizzera italiana

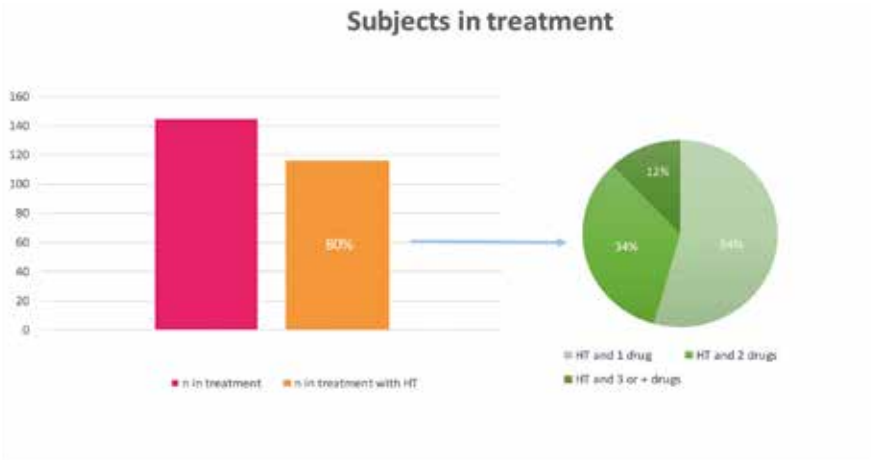


**Fig. 2:** Percentage of subjects in treatment not reaching target blood pressure values (orange) broken down by number of medications taken (pie chart).

sure of 124 mmHg, and nighttime systolic blood pressure of 116 mmHg (**Fig 2**). We considered a subject hypertensive whether there were one or more of the following criteria: an office systolic blood pressure (BP) of ≥140 mmHg and/or diastolic BP of ≥90 mmHg or a systolic daytime ABPM ≥ 135 mmHg and/or nighttime ABPM ≥ 120 mmHg or a systolic 24h ABPM ≥ 130 mmHg and/or diastolic ≥ 80 mmHg.

## Discussion

The present study provides critical insights into the prevalence and management of hypertension in the examined population. According to the 2024 ESC and 2023 ESH guidelines more than 40% of the subjects exhibited hypertensive blood pressure levels, emphasizing the widespread nature of this condition and the potential public health implications.

One of the key findings of this study is that one in four individuals with office hypertension presents stress-induced hypertension, characterized by elevated blood pressure in the clinical setting but normal readings in ambulatory monitoring. This underscores the need for accurate diagnostic methods, including ABPM, to differentiate between true hypertension and transient office-induced elevations. Failure to recognize this phenomenon may lead to unnecessary treatment, exposing patients to potential adverse effects without clinical benefit.

Additionally, the study reveals that almost three-quarters of individuals with office hypertension have Grade 1 hypertension. This finding highlights an important opportunity for early intervention, which could significantly impact long-term cardiovascular outcomes. Lifestyle modifications, including dietary adjustments, increased physical activity, and weight management, should be prioritized to prevent progression to more severe hypertension.

A particularly concerning aspect of the study is the high percentage of treated hypertensive individuals who fail to reach target blood pressure levels. Among those receiving monotherapy, 85% remain formally hypertensive, indicating a need for more effective therapeutic strategies, including dose adjustments, or combination therapy. Similarly, 75% of patients on dual therapy and 73% on three or more medications do not achieve adequate blood pressure control. These findings, although referring to the diagnosis and not to the severity of hypertension, suggest that hypertension management requires a more personalized approach, with close monitoring and, potentially, optimization of medication regimens.

The role of the primary care physician is essential in the early detection, assessment, and management of hypertension. Physicians should be equipped to evaluate the reliability of office blood pressure measurements and determine the necessity for additional diagnostic tools such as ABPM. Moreover, they play a pivotal role in guiding patients toward lifestyle modifications and implementing pharmacological interventions when necessary. Regular follow-ups and treatment adjustments based on individual patient responses are crucial for optimizing blood pressure control and minimizing the risk of long-term complications.

In conclusion, this study highlights the high prevalence of hypertension, the challenges in accurate diagnosis, and the substantial proportion of treated individuals who fail to reach target blood pressure levels. A multifaceted approach, incorporating lifestyle interventions, patient education, and tailored pharmacological strategies, is essential for improving hypertension management and reducing its impact on public health.

**Hypertension - prevalence and management efficacy in Southern Switzerland**


## Abstract

Hypertension is a major public health concern worldwide, significantly contributing to cardiovascular morbidity and mortality. This study investigates the prevalence, management, and treatment outcomes of hypertension in the Italian-speaking region of Switzerland. A total of 1,202 individuals participated in the study, undergoing office blood pressure measurements and 24-hour ambulatory blood pressure monitoring.

Results indicate that over 40% of the examined population exhibited hypertensive blood pressure levels according to the 2024 ESC and 2023 ESH guidelines. A key finding is that one in four individuals with office hypertension experienced stress-induced hypertension, highlighting the importance of ambulatory blood pressure monitoring in distinguishing context related elevations from sustained hypertension. Additionally, three-quarters of those diagnosed with office hypertension presented with Grade 1 hypertension, underscoring the need for early intervention through lifestyle modifications and pharmacological treatment when necessary.

Alarmingly, a significant proportion of hypertensive individuals did not receive adequate treatment. Among hypertensive patients, 74% were untreated, and among those undergoing treatment, 80% failed to reach target blood pressure levels. The study found that 85% of patients on monotherapy remained hypertensive, indicating the potential need for combination therapy and treatment optimization.

These findings emphasize the essential role of primary care physicians in diagnosing and managing hypertension effectively. Physicians must ensure accurate blood pressure assessment, promote lifestyle changes, and tailor pharmacological interventions to individual needs. A comprehensive, multifaceted approach incorporating patient education, regular monitoring, and evidence-based treatment strategies is crucial to improving hypertension control and reducing the associated cardiovascular risks. This study highlights the urgent need for enhanced public health strategies to address hypertension and its long-term consequences effectively.


**Keywords:** Hypertension, Prevalence, Management, Treatment efficacy, Switzerland

**References**


1. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, Muiesan ML, Tsioufis K, Agabiti-Rosei E, Algharably EAE, Azizi M, Benetos A, Borghi C, Hitij JB, Cifkova R, Coca A, Cornelissen V, Cruickshank JK, Cunha PG, Danser AHJ, Pinho RM, Delles C, Dominiczak AF, Dorobantu M, Doumas M, Fernández-Alfonso MS, Halimi JM, Járai Z, Jelakovi B, Jordan J, Kuznetsova T, Laurent S, Lovic D, Lurbe E, Mahfoud F, Manolis A, Miglinas M, Narkiewicz K, Niiranen T, Palatini P, Parati G, Pathak A, Persu A, Polonia J, Redon J, Sarafidis P, Schmieder R, Spronck B, Stabouli S, Stergiou G, Taddei S, Thomopoulos C, Tomaszewski M, Van de Borne P, Wanner C, Weber T, Williams B, Zhang ZY, Kjeldsen SE. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023;41(12):1874-2071.
2. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71(6):1269-1324.
3. Gaziano TA, Bitton A, Anand S, Weinstein MC; International Society of Hypertension. The global cost of nonoptimal blood pressure. J Hypertens. 2009;27(7):1472-1477.
4. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020;16(4):223-237.
5. Walther D, Curjuric I, Dratva J, Schaffner E, Quinto C, Rochat T, Gaspoz JM, Burdet L, Bridevaux PO, Pons M, Gerbase MW, Schindler C, Probst-Hensch N. High blood pressure: prevalence and adherence to guidelines in a population-based cohort. Swiss Med Wkly. 2016;146:w14323.
6. Damianaki A, Wang W, Beaney T, Burkard T, Sudano I, Burnier M, Wuerzner G. May measurement month 2017-2019: results from Switzerland. Eur Heart J Suppl. 2022;24(Suppl F):F38-F40.
7. Malik FT, Al Mamun MA, Ishraquzzaman M, Kalimuddin M, Shahriar Huq T, Rahman MS, Choudhury SR, Ahmed N, Badiuzzaman M, Beaney T, Xia X, Ster AC, Malik A, Poulter NR. May measurement month 2018: an analysis of blood pressure screening results from Bangladesh. Eur Heart J Suppl. 2020;22(Suppl H):H20-H22.
8. Fidalgo ASQ, Vollenweider P, Marques-Vidal P. Ten-year incidence of hypertension in a Swiss population-based sample Incidence of hypertension in Switzerland. J Hum Hypertens. 2019;33(2):115-122.
9. Huang Y, Huang W, Mai W, Cai X, An D, Liu Z, Huang H, Zeng J, Hu Y, Xu D. White-coat hypertension is a risk factor for cardiovascular diseases and total mortality. J Hypertens. 2017;35(4):677-688.
10. Huart J, Persu A, Lengelé JP, Krzesinski JM, Jouret F, Stergiou GS. Pathophysiology of the nondipping blood pressure pattern. Hypertension. 2023;80(4):719-729.
11. Marques-Vidal P, Maung KK, Gouveia A. Twenty-year trends of potentially avoidable hospitalizations for hypertension in Switzerland. Hypertens Res. 2024;47(10):2847-2854.
12. Endes S, Schaffner E, Caviezel S, Dratva J, Autenrieth CS, Wanner M, Martin B, Stolz D, Pons M, Turk A, Bettschart R, Schindler C, Künzli N, Probst-Hensch N, Schmidt-Trucksäss A. Physical activity is associated with lower arterial stiffness in older adults: results of the SAPALDIA 3 Cohort Study. Eur J Epidemiol.

2016;31(3):275-285.
13. Marques-Vidal P, Paccaud F. Regional differences in self-reported screening, prevalence and management of cardiovascular risk factors in Switzerland. BMC Public Health. 2012;12:246.
14. Del Giorno R, Troiani C, Gabutti S, Stefanelli K, Gabutti L. Comparing oscillometric and tonometric methods to assess pulse wave velocity: a population-based study. Ann Med. 2021;53(1):1-16.
15. Shimada K, Kawamoto A, Matsubayashi K, Ozawa T. Silent cerebrovascular disease in the elderly. Correlation with ambulatory pressure. Hypertension. 1990;16(6):692-699.

**Affiliations**
Dr. Francesca Cinieri
Servizio di Medicina di Famiglia,
Ente Ospedaliero Cantonale,
6900 Lugano, Svizzera

Dr. Martina Zandonà
Servizio di Medicina di Famiglia,
Ente Ospedaliero Cantonale,
6900 Lugano, Svizzera

Sébastien Sare
Servizio di Medicina di Famiglia,
Ente Ospedaliero Cantonale,
6900 Lugano, Svizzera

Dr. med. Franco Muggli
Istituto di Medicina di Famiglia,
Università della Svizzera Italiana,
6900 Lugano, Svizzera

PD Dr. med. Rosaria Del Giorno
Servizio di Angiologia, Ente Ospedaliero
Cantonale, 6900 Lugano, Svizzera

Prof. Dr. med. Luca Gabutti
Servizio di Medicina di Famiglia,
Ente Ospedaliero Cantonale,
Lugano, Svizzera and Istituto di Medicina di
Famiglia, Università della Svizzera Italiana,
6900 Lugano, Svizzera

Corresponding author: Martina Zandonà,
e-mail: martina.zandona@eoc.ch

**Declarations**
- Authors' role in the preparation of the manuscript: conceptualization, L.G., M.Z., and F.C.; investigation, R.D.G. and L.G.; data curation, M.Z. and R.D.G.; writing—original draft preparation, M.Z., L.G. S.S. and F.C; writing—review and editing, L.G. and F.M. All authors have read and agreed to the published version of the manuscript.
- Conflicts of Interest: the authors declare no conflicts of in-terest.
- Funding: this research received no external funding.
- Ethic: the TEST study was approved by the local Swiss ethics committee (CE 3115-2016-01718).
- Access to raw data: the authors are ready to provide the raw data upon reasonable request.

# Senza calcoli complicati?

La soluzione: 1 volta al giorno, 12 mmol*, 100% citrato[1,2,3]

MAGNESIUM
Diasporal®

**12 mmol***

**Mg**

Magnesio

**solo 1 assunzione ogni 24 ore**

1 DOSE GIORNALIERA[1] — 12 mmol[1*] — A CARICO DELLE CASSE MALATI[4]

Efficacia che si sente.

- **1 dose giornaliera[1,2,3]**
- **12 mmol[1*]**
- **A carico delle casse malati[4]**

| 3 | 4 |
|---|---|
| Li Litio 6.94 | Be Berillio 9.0122 |
| 11 | 12 |
| Na Sodio 22.990 | Mg Magnesio 24.305 |
| 19 | 20 | 21 |
| K Potassio 39.098 | Ca Calcio 40.078 | Sc Scandio 44.956 |


**a carico delle casse malati[4]**

* in base al dosaggio consentito


**Referenze**
**1)** Informazione professionale Magnesium-Diasporal® 300 su www.swissmedicinfo.ch, consultato settembre 2023 **2)** Informazione professionale Magnesium-Diasporal® 100 CitraCaps su www.swissmedicinfo.ch, consultato settembre 2023 **3)** Informazione professionale Magnesium-Diasporal® 300 senza zucchero su www.swissmedicinfo.ch, consultato settembre 2023 **4)** Elenco delle specialità dell'UFSP su www.spezialitaetenliste.ch, aggiornato a settembre 2023. Possiamo fornire tutte le referenze su richiesta.


Informazione professionale sintetica: Magnesium-Diasporal® 100 CitraCaps, capsule / Magnesium- Diasporal® 300, Granulato / Magnesium-Diasporal® 300 senza zucchero, granulato. **Principio attivo:** Magnesium ut Magnesii citras; 100 mg di magnesio (= 4,0 mmol) per capsula o 301 mg di magnesio (= 12,4 mmol) per bustina. **Indicazioni:** profilassi e terapia delle aritmie tachicardiche, coronaropatia, ipereccitabilità neuromuscolare, tetania, spasmi o crampi muscolari, miosite ossificante profilassi delle recidive dell'urolitiasi da ossalato di calcio, preeclampsia, eclampsia, carenza di magnesio, in caso di maggiore fabbisogno di magnesio. **Posologia:** per adulti e adolescenti dai 12 anni, 3 capsule o 1 bustina al giorno. Durata dell'assunzione: almeno 6 settimane. **Controindicazioni:** insufficienza renale acuta o cronica, diatesi da calcoli di fosfato di magnesio-ammonio, essiccosi. **Precauzioni:** in caso di bradicardia per alterata conduzione dello stimolo cardiaco, ridotta funzionalità renale. **Interazioni:** tetracicline, fluoruri, colecalciferolo. **Gravidanza/allattamento:** assunzione consentita. **Effetti indesiderati:** occasionalmente feci molli. **Confezioni:** confezione da 120 capsule o 20 e 50 bustine; categoria di dispensazione: B; a carico dalle casse malati; Doetsch Grether SA, 4051 Basilea; stato dell'informazione: agosto 2017. Informazioni dettagliate al sito www.swissmedicinfo.ch.


**DOETSCH GRETHER SA, 4051 Basilea, tel. 061 287 34 11, info@doetschgrether.ch, www.doetschgrether.ch**


DOETSCH GRETHER


DG.R.03.092023.9

A cura dell'Istituto
di medicina
di famiglia USI

Università della Svizzera italiana

# INTOSSICAZIONE DA MONOSSIDO DI CARBONIO: CAUSE EMERGENTI E MISCONOSCIUTE

Gabriel Bronz, Fabio Lanzi,
Michael Llamas, Adam Ogna

Ricevuto: 7 aprile 2025,
revisionato: 16 aprile 2025,
accettato: 27 aprile 2025



ISSN print: 1421-1009
ISSN online: 3042-6138

DOI: 10.63648/sfcpyb66

## Introduzione

Il monossido di carbonio (CO) è un gas inodore e incolore prodotto dalla combustione incompleta degli idrocarburi, tra cui carbone, legno, e derivati del petrolio (**figura 1**). Sebbene le fonti più note di esposizione al CO siano gli incendi, sempre più frequentemente si verificano delle intossicazioni in cui la sorgente non è nota né al paziente né al medico. Lo scopo di questa review narrativa è quello di ricapitolare brevemente la patofisiologia dell'intossicazione da CO e sensibilizzare sulle cause meno note.

## Patofisiologia

Una volta inalato, il CO si lega all'emoglobina con un'affinità 200 volte superiore a quella dell'ossigeno, formando la carbossiemoglobina e compromettendo il trasporto di ossigeno senza alterare la pressione parziale dell'ossigeno stesso e dell'anidride carbonica [1].
La ventilazione è regolata dai chemorecettori centrali e periferici sensibili alle variazioni di pH, pressione parziale di ossigeno e anidride carbonica. Poiché quest'ultimi due parametri restano stabili nell'intossicazione da CO, non si attiva il riflesso della dispnea, dando luogo alla cosiddetta "ipossiemia silenziosa".
In situazioni normali, l'emoglobina legata all'ossigeno appare rossa, quella deossigenata blu. La cianosi compare con >40–50 g/L di emoglobina deossigenata. Nell'intossicazione da CO, la carbossiemoglobina appare di un colore rosso-ciliegio, mascherando la comparsa della cianosi.
Infine, una volta raggiunti i tessuti, il CO esercita la sua tossicità legandosi al citocromo C mitocondriale, inibendo la catena respiratoria e compromettendo la produzione di ATP [2].

## Le difficoltà diagnostiche

Definito il "camaleonte del pronto soccorso" o il "killer silenzioso", il CO induce una sintomatologia aspecifica che può mimare un'influenza, un'intossicazione alimentare, una sindrome vertiginosa, una sindrome coronarica acuta o una crisi epilettica [3].
L'assenza di segni patognomonici e la somiglianza con altre patologie ne ritardano spesso la diagnosi, soprattutto in assenza di una fonte evidente come può esserlo un incendio [4].
La diagnosi è ulteriormente ostacolata dal limite dei pulsossimetri convenzionali, incapaci di distinguere tra ossiemoglobina e carbossiemoglobina. Sebbene siano stati sviluppati dei pulsossimetri in grado di misurare la carbossiemoglobina, il loro utilizzo non è ancora diffuso.
Infine, la mancanza di dispnea o cianosi può mascherare l'ipossia tissutale, inducendo a sottovalutare la gravità dell'intossicazione.

## Metodo

È stata condotta una review della letteratura tramite ricerca nel database National Library of Medicine, utilizzando i seguenti termini: "occult carbon monoxide poisoning" OPPURE "hidden carbon monoxide poisoning" OPPURE "silent carbon monoxide poisoning".

## Risultati

Le intossicazioni da CO sono riportate in letteratura soprattutto sotto for-

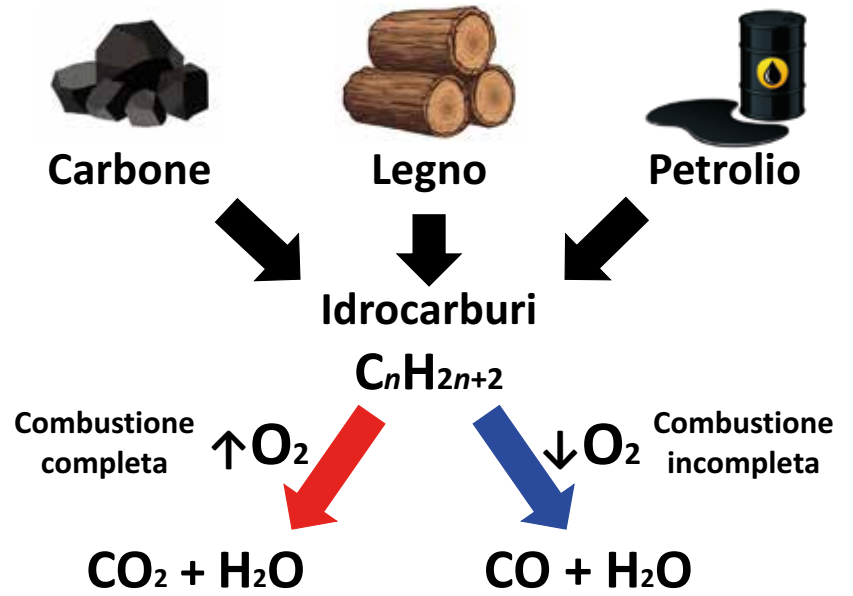


**Fig. 1:** principali fonti di monossido di carbonio (CO). La combustione completa degli idrocarburi (formula chimica $C_nH_{2n+2}$), produce anidride carbonica ($CO_2$) e acqua ($H_2O$), mentre la combustione incompleta, che si verifica quando l'ossigeno ($O_2$) disponibile è insufficiente, porta alla formazione di CO.

| |
|---|
| Fonti domestiche (caldaie, scaldabagni, stufe, forni, camini) e riscaldamenti esterni (funghi riscaldanti) |
| Gas di scarico dei mezzi a motore (automobili, moto, motorini, tagliaerba) |
| Attività sportive e ricreative (mud bogging, piste di ghiaccio al coperto) |
| Barbecue |
| Generatori portatili di elettricità |
| Narghilé |
| Fumo di sigaretta |

**Tab. 1:** fonti emergenti e misconosciute di intossicazione da monossido di carbonio.

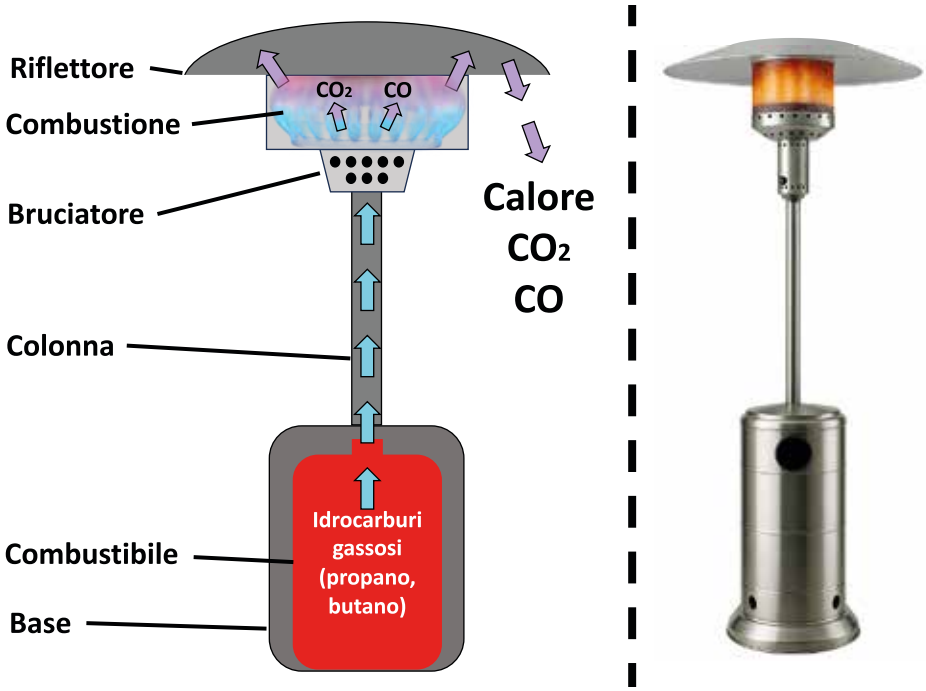


**Fig. 2:** schema di funzionamento del fungo riscaldante. Il gas della bombola viene acceso nel bruciatore, innescando la reazione di combustione che produce calore e anidride carbonica ($CO_2$). Il calore viene irradiato nell'ambiente attraverso il riflettore. In caso di scarsa ventilazione o combustione incompleta, può formarsi il monossido di carbonio (CO).

ma di case reports e case series. Il nostro lavoro di revisione ha permesso di identificare una serie di cause emergenti e misconosciute che descriviamo di seguito (**tabella 1**).

**Fonti domestiche (caldaie, scaldabagni, stufe, forni, camini) e riscaldamenti esterni (funghi riscaldanti)**

L'intossicazione da CO può derivare dalla combustione incompleta di combustibili liquidi (kerosene), gassosi (metano, propano, butano) o solidi (carbone, legna, pellet). Questi sono usati in caldaie, stufe, forni, camini e dispositivi per il riscaldamento esterno (come i funghi riscaldanti, **figura 2**). Malfunzionamenti, scarsa ventilazione o assenza di sistemi di sicurezza possono favorire l'accumulo del CO. Sebbene l'uso domestico di questi combustibili sia in calo nei paesi occidentali, resta frequente nelle cascine delle nostre valli e nei paesi in via di sviluppo [5]. A complicare l'identificazione della sorgente in questi casi è il fatto che il CO è in grado di attraversare le pareti porose (come quelle in legno o cartongesso), muri poco isolati, crepe o fessure, causando intossicazioni in ambienti adiacenti [6].

**Gas di scarico dei mezzi a motore (automobili, moto, motorini, tagliaerba)**

Il CO è uno dei componenti principali dei gas di scarico dei veicoli motorizzati. Le intossicazioni si verificano generalmente in ambienti chiusi e scarsamente ventilati (in particolare quando il motore rimane acceso o se vi sono delle perdite dal sistema di scarico) o in ambienti estremamente trafficati. Inoltre, anomalie nei sistemi di riscaldamento dell'automobile possono favorire l'ingresso di CO nell'abitacolo. Le categorie professionali maggiormente a rischio comprendono meccanici, garagisti, giardinieri, conducenti di autobus e operatori stradali [7].

**Attività sportive e ricreative**

Nel "mud bogging" (uno sport fuoristrada su piste fangose), i veicoli spesso si bloccano nel fango, con conseguente ostruzione dello scarico e rischio di diffusione di CO nell'abitacolo [8]. Le macchine rasaghiaccio a combustibile, usate per levigare le piste di hockey o pattinaggio, possono generare elevate quantità di CO che si può accumulare in ambienti coperti e poco ventilati [9].

**Barbecue**

Il barbecue è un metodo di cottura che utilizza fuoco diretto o calore indiretto per grigliare. Carbone, legna, o gas sono le fonti di calore solitamente utilizzate. L'uso di barbecue portatili in spazi chiusi come tende, garage, roulotte, o appartamenti può trasformare un momento conviviale in un pericolo mortale [10].

**Generatori portatili di elettricità**

I generatori portatili di elettricità so-

A cura dell'Istituto
di medicina
di famiglia USI

no dispositivi a combustione interna progettati per fornire energia elettrica in assenza di una fonte di alimentazione fissa. Se impiegati in ambienti chiusi o scarsamente ventilati, possono generare elevate concentrazioni di CO [11].

**Narghilé**

Il narghilé, noto anche come "water pipe" o "shisha", è una pratica di fumare il tabacco originaria del Medio Oriente. Degli appositi carboncini vengono accesi a bassa fiamma e posti su un foglio di alluminio: la loro combustione genera elevate quantità di CO e di anidride carbonica. Il fumo prodotto viene aspirato, passando prima attraverso il tabacco e dopo attraverso l'acqua dell'ampolla che dovrebbe agire da filtro (**figura 3**). L'effetto filtro risulta però scarso: l'anidride carbonica viene trattenuta nell'acqua in quanto polare, ma il CO, essendo lipofilo, non viene filtrato e viene liberato nell'inalato. Un ulteriore fattore di rischio di tale pratica è la lunga durata d'esposizione (una sessione dura 30-90 minuti) [4].

**Fumo di sigaretta**

Il fumo di sigaretta comporta un'esposizione cronica a basse concentrazioni di CO, con livelli di carbossiemoglobina che possono avvicinarsi al 10% (nel soggetto che non fuma il tasso non supera il 5%). Il fumo di sigaretta rappresenta sovente un fattore confondente che complica l'interpretazione degli esami strumentali in presenza di un sospetto di intossicazione da CO. Il consumo di sigarette in ambienti chiusi o scarsamente ventilati, come può accadere durante incontri serali tra giovani a casa o in locali affollati, può far aumentare la concentrazione di CO. Questa condizione espone anche chi non fuma al rischio di intossicazione [12].

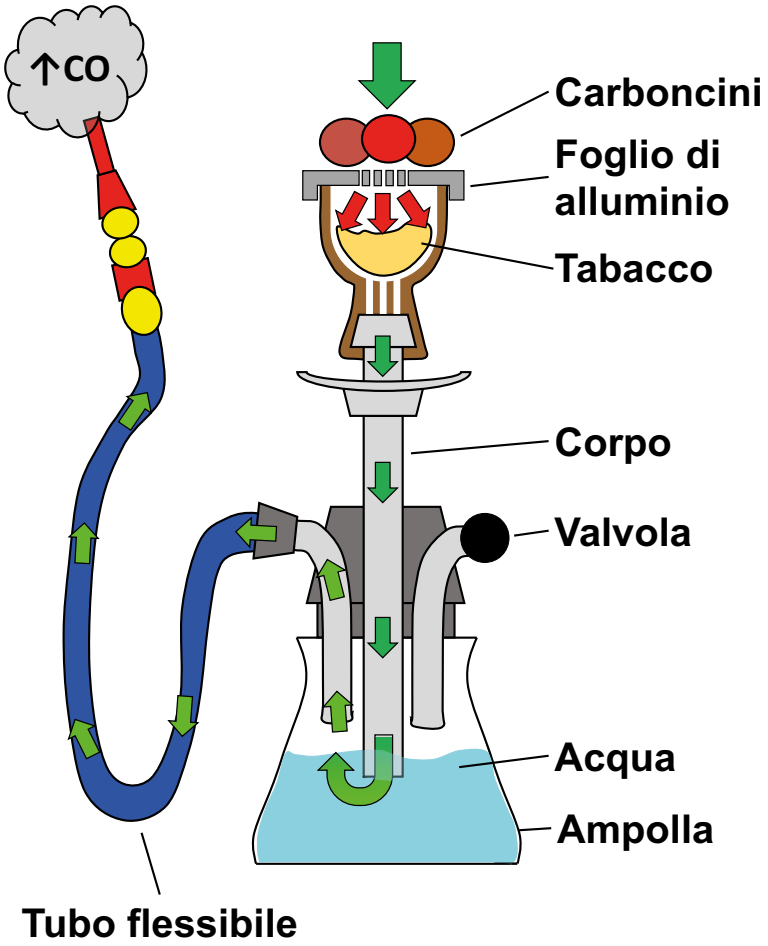


**Fig. 3:** schema del funzionamento del narghilé. Il fumo aspirato passa attraverso l'acqua che, però, non riesce a filtrare il monossido di carbonio (CO), il quale viene liberato nell'inalato e dove raggiunge concentrazioni elevate alle quali viene esposto il fumatore.

**Discussione**

L'intossicazione da CO è un'urgenza insidiosa spesso sottodiagnostica. In Svizzera si registrano ogni anno circa un centinaio di casi.

Fino agli anni Ottanta, l'uso diffuso del gas manifatturiero, dei dispositivi a combustione, e del kerosene costituiva la fonte principale di intossicazione nei paesi occidentali. Diversi studi tra gli anni Ottanta e Novanta documentarono un incremento dei casi di intossicazione da CO durante i mesi invernali, spesso collegati all'uso di sistemi di riscaldamento domestico. Tali casi coinvolgevano fino al 20% dei pazienti che si presentavano in pronto soccorso per disturbi simil-influenzali, dolore toracico, alterazione dello stato di coscienza, o convulsioni [13]. Grazie ai progressi tecnologici e ai meccanismi di sicurezza, la loro incidenza si è ridotta, ma tali dispositivi rimangono ancora utilizzati nei paesi in via di sviluppo e nelle abitazioni di montagna. La presenza di più persone nella stessa abitazione con sintomatologia non-specifica, soprattutto nel periodo invernale, deve suggerire una possibile fuga di CO da uno di questi dispositivi.

Diversamente, altre fonti di intossicazione, quali i gas di scarico dei motori a combustione, l'uso di barbecue e di generatori di elettricità portatili senza rispetto delle misure di sicurezza, continuano a rappresentare un rischio significativo. Studi condotti su lavoratori di garage automobilistici e

su autisti di autobus hanno rilevato una prevalenza d'intossicazione occulta da CO fino al 30% delle persone testate [7; 14]. Inoltre, l'uso di barbecue in ambienti chiusi o scarsamente ventilati è stato responsabile di numerosi casi d'intossicazione, spesso con esiti fatali [10]. Tra il 2008 e il 2011 negli Stati Uniti d'America sono stati documentati oltre 200 casi d'intossicazione da generatori di elettricità portatili [11].

Un aspetto meno noto delle intossicazioni da CO riguarda l'esposizione in contesti sportivi e ricreativi. Particolare attenzione meritano le intossicazioni correlate al "mud bogging" e alle attività su piste di ghiaccio [8]. Il miglioramento della ventilazione o l'impiego di macchine rasaghiaccio elettriche (come avviene nelle arene del Hockey Club Lugano e dell'Ambrì-Piotta) ha contribuito a ridurre il rischio di intossicazione. Tuttavia, nelle strutture che continuano a impiegare macchine rasaghiaccio a combustione, così come per chi partecipa a competizioni di mud bogging, è imprescindibile mantenere un elevato indice di sospetto clinico: la comparsa di sintomi non-specifici successivi alla permanenza in tali ambienti deve allarmare.

Infine, la diffusione del narghilè ha il potenziale di trasformarsi in un vero pericolo per la salute pubblica [15]. A testimonianza della sua diffusione, vi è il fatto che almeno due terzi dei casi riportati in letteratura provengono dai paesi occidentali. A favorirne il suo uso vi è verosimilmente la falsa percezione della sua innocuità rispetto al fumo di sigaretta [16]. In realtà, una sessione di narghilè espone ad un carico di CO fino a 10 volte superiore rispetto a una sigaretta [4]. Anche la stessa sigaretta, però, se fumata in un ambiente poco ventilato, aumenta il rischio di intossicazione [12].

Date le difficoltà diagnostiche, l'implementazione di un esame di screening in pronto soccorso consentirebbe un'identificazione precoce di questa intossicazione. La misurazione della carbossiemoglobina tramite gasometria si è rivelata una strategia di screening inefficace in termini costo-beneficio [17]. Un'alternativa più pratica ed economicamente sostenibile è rappresentata dall'impiego di pulsossimetri in grado di misurare la carbossiemoglobina già in fase di triage [18]. In Svizzera Italiana, il personale di soccorso pre-ospedaliero è dotato di dispositivi per monitorare la presenza di CO ambientale e di pulsossimetri portatili per misurare la carbossiemoglobina.

Il trattamento si basa sulla somministrazione di ossigeno al 100% (normo- o iperbarico). Rimane controversa l'effettiva utilità dell'ossigenoterapia iperbarica nel prevenire le sequele neuropsichiatriche tardive. L'efficacia dell'ossigenoterapia nel prevenire tali sequele sembra dipendere soprattutto dalla precocità della sua somministrazione, piuttosto che dalla modalità con cui viene erogata [19]. Nonostante non esista un consensus univoco, la maggior parte delle linee guida raccomanda l'ossigenoterapia iperbarica nelle seguenti situazioni: valori di carbossiemoglobina ≥25%, casi gravi (sincope, dolore toracico, convulsioni, deficit neurologici) o gravidanza [20]. Sebbene anche i pazienti pediatrici possono essere coinvolti in intossicazioni da CO, non esistono guidelines ufficiali per questa fascia d'età ed ogni caso deve essere valutato singolarmente.

La decisione terapeutica finale è influenzata spesso dall'accessibilità alla camera iperbarica, questo però non deve ritardare la somministrazione precoce di ossigeno. In Svizzera Italiana esiste una camera iperbarica mobile attivabile via 144.

## Conclusioni

L'intossicazione acuta da CO costituisce una condizione insidiosa, sottodiagnosticata e potenzialmente letale. Si raccomanda di sensibilizzare il personale sanitario al riconoscimento precoce dei sintomi e integrare progressivamente mezzi diagnostici avanzati, come ad esempio pulsossimetri capaci di misurare sia l'ossiemoglobina che la carbossiemoglobina per evitare di ritardare o mancare la diagnosi di questa intossicazione.

## Carbon monoxide poisoning: emerging and overlooked causes


### Abstract

Carbon monoxide poisoning is a subtle and insidious medical emergency. Due to its ability to mimic other conditions such as influenza, food poisoning, vestibular disorders, acute coronary syndrome, or epileptic seizures, it has been referred to as the "chameleon of emergencies". While fires are a well-recognized source of carbon monoxide exposure, cases in which the origin remains unknown to both physicians and patients are increasingly reported. To enhance awareness of emerging and overlooked sources of carbon monoxide poisoning and summarize its pathophysiology, we conducted a comprehensive review in the National Library of Medicine. The toxicity of carbon monoxide relies on impaired blood oxygen transport and inhibition of the mitochondrial respiratory chain in the tissues. Less recognized sources include domestic combustion appliances (boilers, water heaters, stoves, ovens, and fireplaces), external heating sources (heating mushrooms), motor vehicle exhaust (cars, motorcycles, scooters, lawnmowers), sports-related activities (mud bogging, ice resurfacing machines), misuse of barbecues, portable power generators, and the use of narghile and cigarettes. Given the nonspecific presentation of carbon monoxide poisoning, improving recognition and diagnostic strategies is essential. Greater awareness among healthcare professionals, along with the integration of advanced diagnostic tools such as pulse

A cura dell'Istituto
di medicina
di famiglia USI

oximeters capable of measuring carboxyhemoglobin levels, could facilitate earlier diagnosis and improve patient outcomes.

**Keywords:** "carbon monoxide poisoning", "occult carbon monoxide", "hidden carbon monoxide"

**Bibliografia**

1. Mak TW, Kam CW, Lai JP, Tang CM. Management of carbon monoxide poisoning using oxygen therapy. Hong Kong Med J. 2000;6(1):113-115.
2. Rose JJ, Wang L, Xu Q, McTiernan CF, Shiva S, Tejero J, Gladwin MT. Carbon monoxide poisoning: pathogenesis, management, and future directions of therapy. Am J Respir Crit Care Med. 2017;195(5):596-606.
3. Long IJ, Flaherty GT. Silent killer-the dangers of carbon monoxide poisoning during international travel. J Travel Med. 2017;24(3):1-3.
4. Bronz G, Lanzi F, Llamas M, Ogna A. Intossicazione acuta da monossido di carbonio: non tutto il mal vien … dalla caldaia ... o dal mosto d'uva. Trib Med Ticin. 2024;89(7-8):117-118.
5. Fisher J, Rubin KP. Occult carbon monoxide poisoning. Arch Intern Med. 1982;142(7):1270-1271.
6. Vermesi I, Restuccia F, Walker-Ravena C and Rein G. Carbon monoxide diffusion through porous walls: evidence found in incidents and experimental studies. Front Built Environ. 2018;4:44.
7. Bol O, Koyuncu S, Günay N. Prevalence of hidden carbon monoxide poisoning in auto service workers; a prospective cohort study. J Occup Med Toxicol. 2018;13:35.
8. Menke NB, Fitzpatrick K, Lynch MJ, King AM. Carbon monoxide poisoning due to "mud bogging". N Engl J Med. 2015;373(11):1082.
9. Eichner ER. Accidental carbon monoxide poisoning in sports and other settings. Curr Sports Med Rep. 2018;17(3):78-79.
10. Gasman JD, Varon J, Gardner JP. Revenge of the barbecue grill. Carbon monoxide poisoning. West J Med. 1990;153(6):656-657.
11. Hampson NB, Dunn SL. Carbon monoxide poisoning from portable electrical generators. J Emerg Med. 2015;49(2):125-129.
12. Goniewicz ML, Kosmider L, Delijewski M, Knysak J, Ochota P, Sobczak A. The impact of the 2010 Polish smoke-free legislation on the popularity and sales of electronic cigarettes. Eur J Public Health. 2014;24(3):471-473.
13. Heckerling PS, Leikin JB, Terzian CG, Maturen A. Occult carbon monoxide poisoning in patients with neurologic illness. J Toxicol Clin Toxicol. 1990;28(1):29-44.
14. Abdollahi M, Zadparvar L, Ayatollahi B, Baradaran M, Nikfar S, Hastaie P, Khorasani R. Hazard from carbon monoxide poisoning for bus drivers in Tehran, Iran. Bull Environ Contam Toxicol. 1998;61(2):210-215.
15. de Suremain N, Ngo J, Loschi S, Haegy-Doehring I, Aroulandom J, Carbajal R. Carbon monoxide poisoning from water-pipe (narghile) smoking in a child. Arch Pediatr. 2019;26(1):44-47.
16. Wackowski OA, Hammond D, O'Connor RJ, Strasser AA, Delnevo CD. Smokers' and e-cigarette users' perceptions about e-cigarette warning statements. Int J Environ Res Public Health. 2016;13(7):655.
17. Heckerling PS, Leikin JB, Maturen A, Terzian CG, Segarra DP. Screening hospital admissions from the emergency department for occult carbon monoxide poisoning. Am J Emerg Med. 1990;8(4):301-304.
18. Suner S, Partridge R, Sucov A, Valente J, Chee K, Hughes A, Jay G. Non-invasive pulse CO-oximetry screening in the emergency department identifies occult carbon monoxide toxicity. J Emerg Med. 2008;34(4):441-450.
19. Cowl CT. Justifying hyperbaric oxygen delivery for carbon monoxide poisoning: time to respond to pressure with a large-scale randomized controlled trial. Chest. 2017;152(5):911-913.
20. Mathieu D, Marroni A, Kot J. Tenth European Consensus Conference on Hyperbaric Medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. Diving Hyperb Med. 2017;47(1):24-32.

**Affiliazioni**
Dr. med. Gabriel Bronz
Servizio di medicina interna, Ospedale La Carità, Ente Ospedaliero Cantonale
6600 Locarno (Svizzera)

Dr. med. Fabio Lanzi
Servizio di medicina intensiva, Ospedale La Carità, Ente Ospedaliero Cantonale
6600 Locarno (Svizzera)

Dr. med. Michael Llamas
Servizio di medicina intensiva, Ospedale La Carità, Ente Ospedaliero Cantonale
Servizio di medicina interna, Ospedale La Carità, Ente Ospedaliero Cantonale
6600 Locarno (Svizzera)

Prof. Dr. med. Adam Ogna
Facoltà di scienze biomediche, Università della Svizzera italiana
Servizio di medicina interna, Ospedale La Carità, Ente Ospedaliero Cantonale
6600 Locarno (Svizzera)

Autore corrispondente: Gabriel Bronz,
e-mail: gabriel.bronz@eoc.ch

**Dichiarazioni**
- Ruolo degli autori nella preparazione del manoscritto: concettualizzazione: GB, AO; preparazione del manoscritto: GB, FL; tabelle e figura: GB; versione finale: GB, ML, AO.
- Conflitti di interesse: nessuno.
- Fondi e sponsor: nessuno.
- Etica: non necessaria per un articolo di questo tipo.
- Accesso ai dati grezzi: nessun dato grezzo disponibile per questo articolo.

# CEFEPIME E NEUROTOSSICITÀ: UNA COMPLICANZA SOTTOVALUTATA NELLA POPOLAZIONE GERIATRICA

Luca Barelli, Milagros Altagracia Carela Mora, Rosambra Leo, Olivier Giannini, Anna Acchini

Ricevuto: 28 marzo 2025,
revisionato: 30 aprile 2025,
accettato: 30 aprile 2025



ISSN print: 1421-1009
ISSN online: 3042-6138

DOI: 10.63648/sgs6vf29

**Riassunto**

Il cefepime è una cefalosporina di quarta generazione ampiamente utilizzata per il trattamento delle infezioni nosocomiali anche se è nota una potenziale neurotossicità in particolare nei pazienti anziani e fragili. Questa condizione, caratterizzata da alterazioni cognitive e stato confusionale, si manifesta più frequentemente in presenza di insufficienza renale e/o dosaggi non ottimizzati. Questo lavoro presenta due casi di pazienti geriatrici che hanno sviluppato neurotossicità associata al cefepime.

## Introduction

Cefepime, a fourth-generation cephalosporin, acts by inactivating penicillin-binding proteins on bacterial cell walls. Cefepime is recommended as a first-line drug for nosocomial lower respiratory tract infections. However, it has been known that cefepime can cause encephalopathy secondary to neurotoxicity, with an estimated incidence ranging from 1% to 15% (1). The mechanism of cefepime's neurotoxicity is related to antagonism towards the GABA (A) receptor at the blood-brain barrier in a concentration-dependent manner (2). Normally, only 10% of the drug crosses the blood-brain barrier, but in patients with chronic kidney disease, the reduction of membrane proteins and the accumulation of organic acids can increase this percentage up to 45% (3). Despite these effects being well-documented, cases of cefepime-induced encephalopathy continue to be observed and reported in clinical practice, particularly in patients with an estimated glomerular filtration rate (eGFR) ≤ 30 mL/min. Serum cefepime concentrations >20 mcg/mL are frequently associated with an increased risk of neurotoxicity, with a fivefold higher risk of neurological events (4). Symptoms, including encephalopathy, confusion, seizures with electroencephalogram (EEG) abnormalities, aphasia, and hallucinations, typically appear around the fourth day of therapy (5). In this article, we describe two clinical cases of

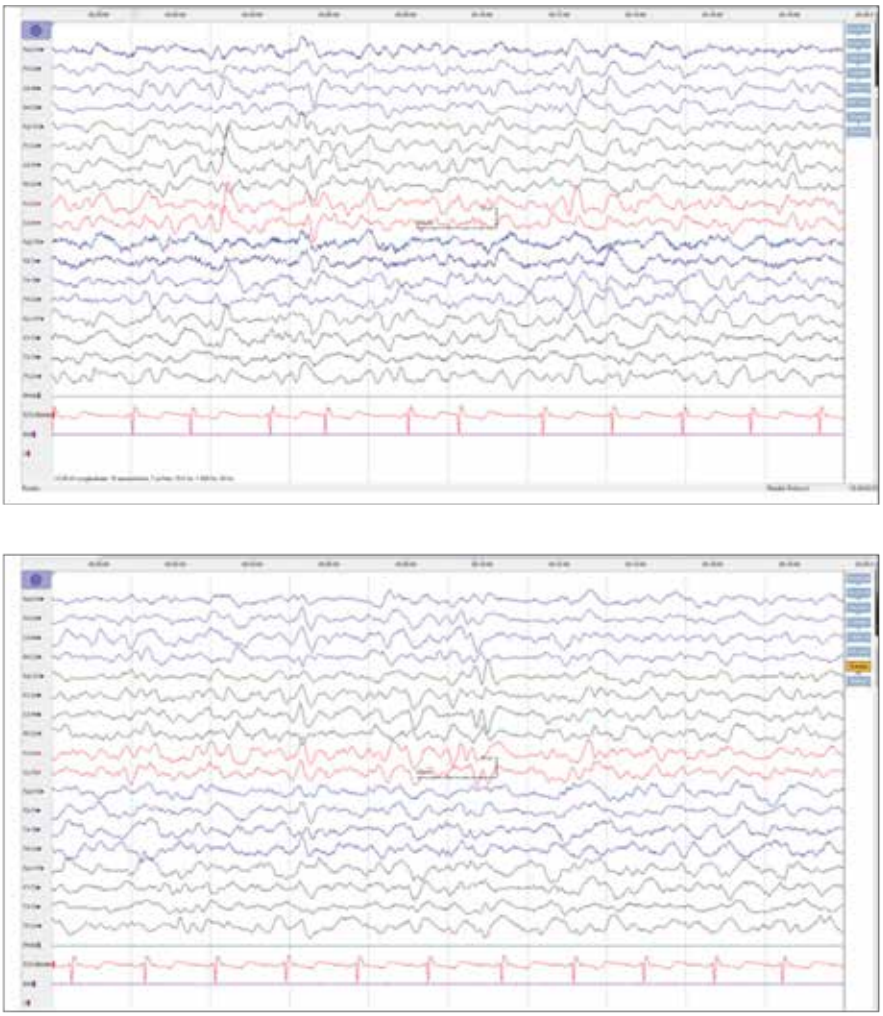

**Fig. 1:** Electroencephalogram (EEG)
The EEG tracing shows a diffuse slowing of the baseline activity with frequent large triphasic waves of diffuse expression. These types of alterations are often associated with moderate-grade diffuse encephalopathy, for example of metabolic origin, compatible with neurotoxicity from cefepime.

A cura dell'Istituto
di medicina
di famiglia USI

cefepime-induced neurotoxicity observed in the Geriatrics Department of the Regional Hospital of Mendrisio.

**Patient 1**
A 91-year-old man with a history of metastatic prostate adenocarcinoma was admitted after two episodes of falls at home, with an inability to get up independently. Radiological examinations ruled out intracranial haemorrhages.

A per protocl for patients admitted under the complex early geriatric rehabilitation program, a neuropsychological screening is performed upon admission which identified deficit of memory, working memory, praxis impairments, fronto-executive dysfunctions, visuospatial difficulties and perceptual deficits that defined a minor neurocognitive disorder.
During hospitalization he developed nosocomial pneumonia and he was treated with intravenous cefepime (2 g 3x/d). The dosage was prescribed based on an estimated glomerular filtration rate (eGFR) of 66 mL/min (CKD-EPI) but renal function adjusted for age and weight or body surface area (BSA) calculated according to the Cockcroft-Gault formula (40 mL/min e 36 mL/min adjusted for BSA) was not taken into account, thereby resulting in a prescribing error.

On the fourth day of therapy, a deterioration in ideomotor function was observed, along with episodes of agitation and confusion, with slowed thinking and drowsiness (the patient is easily awakened but repeats the questions asked without responding). A few days after the onset of the condition, a native brain CT was performed to assess any subacute ischemic lesions, which resulted negative. Given the persistence of the altered state of consciousness, in order to better clarify its origin, an electroencephalogram (EEG) was indicated. The exam revealed background activity with theta and theta-delta waves associated with widespread, non-periodic triphasic waves (**Figure 1**). The electroencephalographic findings are suggestive of a toxic-metabolic cause. After excluding the presence of concurrent metabolic alterations, and considering the recent introduction of Cefepime, the hypothesis of toxicity related to the antibiotic is raised. Discontinuation of the antibiotic led to a gradual clinical improvement and recovery of consciousness.

**Patient 2**
A 77-year-old woman with a known history of arterial hypertension but with no anamnestic evidence of cognitive impairment, she was admitted due to disorientation. The laboratory tests revealed an elevated C-reactive protein level (158 mg/L) and cytolytic and cholestatic hepatopathy. An ultrasound showed a gallstone in the gallbladder without biliary tract dilation. During hospitalization, the patient developed fever (max temperature 38.3°C). An abdominal CT scan

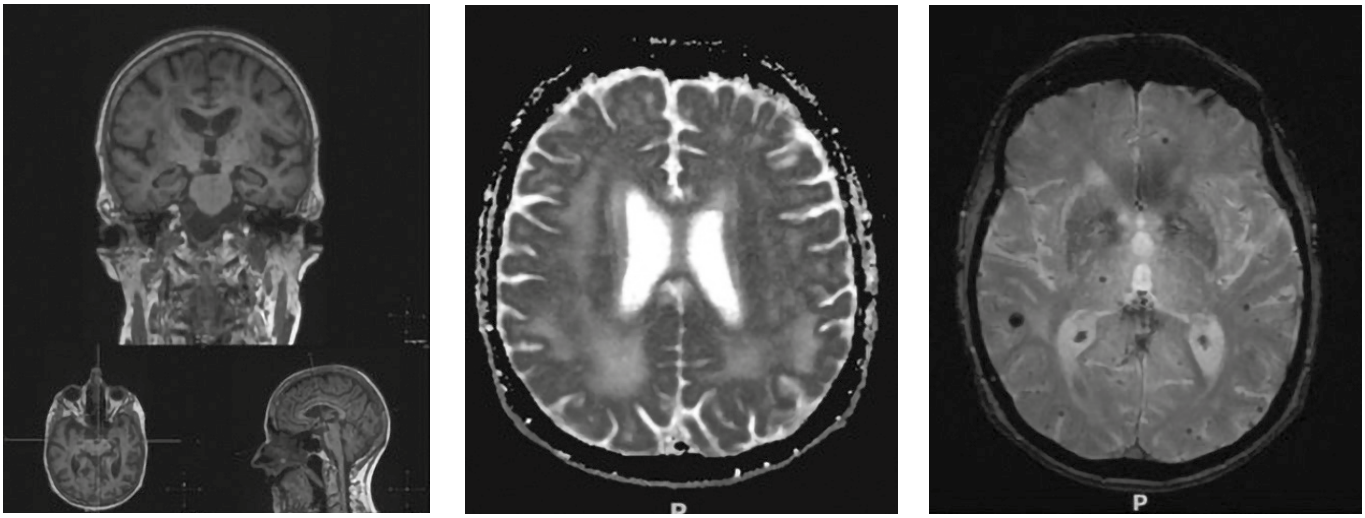


**Fig. 2:** Magnetic Resonance Imaging (MRI) of the brain
1) In the coronal, axial e sagittal slices a reduction in hippocampal volumes is evident in the sections used to calculate the medial temporal atrophy (MTA score 2).
2) This image shows diffuse confluent chronic vascular leukoencephalopathy (Fazekas 3)
3) The axial slices, diffuse lesions consistent with hemosiderin deposits are observed, suggestive of probable cerebral amyloid angiopathy
fepime.

documented a perforated calculous cholecystitis complicated by multiple hypodense hepatic collections. The patient was treated with intravenous cefepime (2 g 3x/d) and metronidazole (500 mg 3x/d), given her normal renal function (93 mL/min/1.73m²). Forty-eight hours after initiating antibiotic therapy, the patient exhibited a slowed speech, anomia, paraphasias, and severe visuospatial and praxic difficulties (Mini Mental State Examination (MMSE) 19/30, cut-off 24; Clock test 3/9). A neuropsychological assessment confirmed significant apraxia, visuospatial and perceptual difficulties. A brain MRI revealed chronic vascular leukoencephalopathy (Fazekas 3), bilateral cortical-subcortical hemosiderin deposits, and areas of mesiotemporal atrophy (MTA score 2) bilaterally (Atrophy is suggestive of Alzheimer's disease AD; however, a CSF analysis was not performed as the cerebrospinal fluid results would not be reliable in this acute phase) (**Figure 2**). Discontinuation of cefepime and substitution with ceftriaxone led to a progressive improvement in cognitive, visuospatial, and perceptual difficulties within 48 hours. A subsequent neuropsychological evaluation showed near-complete recovery, with only mild persistent praxic difficulties (MMSE 28/30; Clock test 7/9).

## Discussion

The presented cases demonstrate that cefepime can cause neurotoxicity in elderly patients even in the absence of preexisting neurocognitive disorders, chronic kidney disease, or prolonged therapy. Cefepime-induced neurotoxicity has been observed within 4–5 days from the start of therapy, although it can occur up to 15 days after its initiation (6). In elderly patients, age-related pharmacokinetic and pharmacodynamic changes increase the risk of toxicity. Therefore, it is crucial to calculate drug dosage based on renal function. Current Recommendations for antibiotic dosing (Swiss monograph, Sanford Guide, UpToDate) according to renal function rely on the Cockcroft-Gault formula, which has been used in the vast majority of drug efficacy and safety studies. Serum cefepime concentrations above 20 mcg/mL have been associated with a high risk of neurotoxicity, considering that the normal therapeutic range is between 5 and 10 mcg/mL (7). A 2017 systematic review showed that 25% of cefepime-induced neurotoxicity cases occurred even in patients who received appropriate dosing (1).

In patients with impaired renal function and those with normal renal function, the initial loading dose of cefepime remains the same. However, maintenance doses should be adjusted based on actual renal function, as described in **Table 3** (8). Elderly patients may exhibit increased sensitivity to drug effects due to receptor and cellular signaling alterations, leading to more pronounced or prolonged responses. These changes require special attention when selecting and dosing medications, as well as regular monitoring to promptly identify signs of toxicity or therapeutic inefficacy.

EEG can aid in assessing neurotoxicity, particularly in settings where therapeutic drug monitoring is not readily available. In toxic-metabolic encephalopathies, EEG is a sensitive but nonspecific tool, typically revealing generalized periodic discharges with triphasic wave morphology (9).

In the first case, calculating clearance using the Cockcroft-Gault formula adjusted for BSA would have indicated an estimated glomerular filtration rate (eGFR) of 36 mL/min/1.73m2, making the administered cefepime dosage excessive. The use of the CKD-EPI value provided by the laboratory led to an error.

In the second case, despite appropriate dosing, neurotoxicity still occurred possibly related to severe vascular encephalopathy with signs of amyloid angiopathy and likely focal

| eGFR* / Infection | >60 | 30-60 | 11-29 | <11 | CAPD | Dialysis |
|---|---|---|---|---|---|---|
| MILD (UTI) | 500mg/12h | 500 mg/24h | 500 mg/24h | 250 mg/24h | 500 mg/48h | 1g on D1, then 500 mg/24h |
| MODERATE (Pneumonia) | 1 gr/12h | 1 gr/24h | 500 mg/24h | 250 mg/24h | 1 g/48h | 1g on D1, then 500 mg/24h |
| SEVERE (Intra-abdominal, complicated UTI or pneumonia) | 2 gr/12h | 2 gr/24h | 1 gr/24h | 500 mg/24h | 2 gr/48h | 1g on D1, then 500 mg/24h |
| FEBRILE NEUTROPENIA | 2 gr/8h | 2 gr/12h | 2 gr/24h | 1gr/24h | 2 gr/48h | 1 gr/ 24h |

**Tab. 3:** Adjustment of Cefepime dosage according to renal function (*eGFR as calculated by the Cockroft-Gault equation)
The table indicates Cefepime dosages adjusted according to renal function for infections of varying severity. Adapted from: Lam S, Gomolin IH. Cefepime neurotoxicity: case report, pharmacokinetic considerations, and literature review. Pharmacotherapy. 2006;26(8):1169-74.

A cura dell'Istituto
di medicina
di famiglia USI

impairment of the blood-brain barrier possibly though a toxicodynamic mechanism.

The underlying pre-existing cognitive condition, as described by neuropsychological assessment and brain imaging, likely played a role in the development of neurotoxicity, identifying this patient population as vulnerable.

A major limitation in these cases is the lack of TDM (Therapeutic Drug Monitoring) results, which makes it unclear whether the toxicity was due to pharmacokinetic variability (e.g., increased drug concentration) or to toxicodynamic susceptibility (neurotoxicity at therapeutic levels).
Given pharmacokinetic variability and the narrow therapeutic window with potential for toxicity, cefepime TDM can be a valuable tool, particularly for vulnerable patient populations such as geriatric and pediatric patients, those with chronic kidney disease (CKD), ICU patients, and those on ECMO. Indeed, the currently recommended dosing regimens may lead to overexposure in geriatric patients.

## Conclusions

Cefepime-induced neurotoxicity is a significant complication in elderly patients. It is crucial to closely monitor renal function, adjust drug dosage accordingly (starting from the first dose) and consider alternative therapies in frail or malnourished patients. The use of TDM can play a crucial role in assessing the appropriate cefepime dosage in these patients. Awareness of these complications allows for the optimization of antibiotic therapy safety and efficacy, reducing the risk of adverse events in a vulnerable population such as the geriatric one. Personalizing pharmacological therapy is essential to maximize benefits and minimize risks, taking into account the specific clinical needs and comorbidities of elderly patients.

## Cefepime and Neurotoxicity An Underestimated Complication in the Geriatric Population

## Abstract

Cefepime is a widely used fourth-generation cephalosporin for the treatment of nosocomial infections but is known for its potential neurotoxicity, particularly in elderly and frail patients. This condition, characterized by cognitive impairment and confusion, occurs more frequently in the presence of renal insufficiency and/or suboptimal dosing. This paper presents two cases of geriatric patients, who developed cefepime-associated neurotoxicity.

**Keywords:** cefepime, neurotoxicity, adverse effect, older patient, geriatrics

### Bibliography

1. Appa AA, Jain R, Rakita RM, Hakimian S, Pottinger PS. Characterizing cefepime neurotoxicity: a systematic review. Open Forum Infect Dis. 2017;4:ofx170.
2. Payne LE, Gagnon GJ, Riker RR, Seder DB, Glisic EK, Morris JC, Fraser GL. Cefepime-induced neurotoxicity: a systematic review. Crit Care. 2017;21:276.
3. Durand-Maugard C, Lemaire-Hurtel AS, Gras-Champel V, Hary L, Maizel J, Prud'homme-Bernardy A, Andréjak C, Andréjak M. Blood and CSF monitoring of cefepime-induced neurotoxicity: nine case reports. J Antimicrob Chemother. 2012;67:1297-9.
4. Huwyler T, Lenggenhager L, Abbas M, Ing Lorenzini K, Hughes S, Huttner B, Karmime A, Uçkay I, von Dach E, Lescuyer P, Harbarth S, Huttner A. Cefepime plasma concentrations and clinical toxicity: a retrospective cohort study. Clin Microbiol Infect. 2017;23:454-9.
5. Deshayes S, Coquerel A, Verdon R. Neurological adverse effects attributable to β-lactam antibiotics: a literature review. Drug Saf. 2017;40:1171-98.
6. Alagha Z, Crow S, Abdeen AMZ, Alastal M, Alastal A. Cefepime neurotoxicity in patients with normal renal function: an overlooked cause of encephalopathy in the intensive care unit. J Investig Med High Impact Case Rep. 2024:12:23247096241259534.
7. Keerty D, Shareef NA, Ramsakal A, Haynes E, Syed M. Cefepime-induced encephalopathy. Cureus. 2021;13:e13125.
8. Lam S, Gomolin IH. Cefepime neurotoxicity: case report, pharmacokinetic considerations, and literature review. Pharmacotherapy. 2006;26:1169-74.
9. Bausch S, Araschmid LJ, Hardmeier M, Osthoff M. Cefepime-induced neurotoxicity in the setting of acute kidney injury: a case series and discussion of preventive measures. Cureus. 2022;14:e26392.

**Affliations**

Luca Barelli
University Department of Geriatric Medicine, Felix Platter, 4055 Basel (Switzerland)

Milagros Altagracia Carela Mora
Geriatric Service, Ente Ospedaliero Cantonale (EOC), Ospedale Regionale della Beata Vergine, Mendrisio (Switzerland) and Department of Medicine, Ente Ospedaliero Cantonale (EOC), 6500 Bellinzona (Switzerland)

Rosambra Leo
University Department of Geriatric Medicine, Felix Platter, 4055 Basel (Switzerland)

Olivier Giannini
Department of Medicine, Ente Ospedaliero Cantonale (EOC), 6500 Bellinzona (Switzerland) and Faculty of Biomedical Sciences, Università della Svizzera italiana (USI), 6900 Lugano (Switzerland)

Anna Acchini
Geriatric Service, Ente Ospedaliero Cantonale (EOC), Ospedale Regionale della Beata Vergine, Mendrisio (Switzerland) and Department of Medicine, Ente Ospedaliero Cantonale (EOC), 6500 Bellinzona (Switzerland)

Corresponding author: Luca Barelli,
e-mail: luca.barelli@felixplatter.ch

**Declarations**

- Authors' role in the preparation of the manuscript: conceptualization: AA, LB, MACM, RL, OG; manuscript preparation: LB, RL, MACM, AA, OG; tables and figures: LB, AA; final version: LB, AA, OG.
- Conflicts of Interest: none
- Funding: this research received no external funding.
- Ethic: since the data are completely anonymous, the research project does not fall within the scope of the law on human research and does not require authorization from the Cantonal Ethics Committee.
- Access to raw data: upon request.