

Review Article

The Diagnosis and Treatment of Carbon Monoxide Poisoning

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Summary

Background: The symptoms of carbon monoxide (CO) poisoning are nonspecific, ranging from dizziness and headache to unconsciousness and death. A German national guideline on the diagnosis and treatment of this condition is lacking at present.

Method: This review is based on a selective literature search in the PubMed and Cochrane databases, as well as on existing guidelines from abroad and expert recommendations on diagnosis and treatment.

Results: The initiation of 100% oxygen breathing as early as possible is the most important treatment for carbon monoxide poisoning. In case of CO poisoning, the reduced oxygen-carrying capacity of the blood, impairment of the cellular respiratory chain, and immune-modulating processes can lead to tissue injury in the myocardium and brain even after lowering of the carboxyhemoglobin (COHb) concentration. In patients with severe carbon monoxide poisoning, an ECG should be obtained and biomarkers for cardiac ischemia should be measured. Hyperbaric oxygen therapy (HBOT) should be critically considered and initiated within six hours in patients with neurologic deficits, unconsciousness, cardiac ischemia, pregnancy, and/or a very high COHb concentration. At present, there is no general recommendation for HBOT, in view of the heterogeneous state of the evidence from multiple trials. Therapeutic decision-making is directed toward the avoidance of sequelae such as cognitive dysfunction and cardiac complications, and the reduction of mortality. Smoke intoxication must be considered in the differential diagnosis. The state of the evidence on the diagnosis and treatment of this condition is not entirely clear. Alternative or supplementary pharmacological treatments now exist only on an experimental basis.

Conclusion: High-quality, prospective, randomized trials that would enable a definitive judgment of the efficacy of HBOT are currently lacking.

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Carbon monoxide (CO) at low concentrations is an odorless and colorless gas with a molecular weight that is similar to that of air. It develops in incomplete combustion processes of substances containing carbon (e1). In addition to fires, defect gas boilers, or wood pellet storage facilities, the risk of poisoning as a result of smoking hookah has become a focus in recent years (1, e2). Relevant alerting key words and the use of portable CO meters are intended to raise awareness in rescue personnel.

In the USA, 20 000–50 000 cases of carbon monoxide poisoning occur every year (2). Treatment for accidental carbon monoxide poisoning costs the US healthcare system some \$1.3 billion every year (e3). For Germany, the only available data are those from the German Federal Statistical Office, for inpatients and deaths with a diagnosis of CO intoxication (T58 in ICD-10) (e4). In the USA, the total number of deaths due to CO poisoning fell between 1999 and 2014 (from 1967 cases to 1319 cases) (e5), whereas in Germany, numbers have steadily risen in recent years. In 2015, 648 patients died as a result of CO poisoning (0.8 deaths/100 000 population) (eTable). Fatality depends on exposure times to CO and its concentrations and is crucially affected by the toxicity of further gases involved (comparative case series [3]).

Pathophysiology

Carbon monoxide diffuses rapidly through the alveolar membrane and binds with an affinity that is 230–300 times that of oxygen, preferably to the iron ion in heme. Conformation changes lead to a leftward shift in the position of the oxyhemoglobin dissociation curve, to reduced oxygen transport capacity, and to reduced oxygen release into the peripheral tissue (2). Within tissue, CO also binds to other heme-containing proteins, such as skeletal and myocardial myoglobin. Since elimination times in tissue and blood differ (e7), tissue injury can also develop with a delay.

At the cellular level, carbon monoxide leads—among others—to an activation of neutrophils, to a proliferation of lymphocytes, to mitochondrial dysfunction, and to lipid peroxidation (2, 4). The development of oxygen radicals, oxidative stress, inflammation, and apoptosis is comparable to a reperfusion injury and constitutes a substantial damage mechanism (2, 5, 6).

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TABLE 1

Selection of larger studies of the effects of carbon monoxide on the health of patients

First author/year	Design	Time period	Intervention/variable	Result	N	Comment
Satran 2005 (13)	Retrospective cohort study	1994–2002	All patients with HBO, 1 course of treatment (2.4 atm)	37% of patients with CO intoxication had raised cardiac biomarkers or ECG changes, in-hospital mortality was 5%,	230	Cohort identical to Henry (14)
Henry 2006 (14)	Prospective cohort study	1994–2005	All patients with HBO, 1 course of treatment (2.4 atm)	Myocardial injury as a significant predictor for mortality in the 7.6 year observation period (AHR 2.1; 95% CI [1.2; 3.7])	230	Cohort identical to Satran (13)
Huang 2014 (17)	Longitudinal cohort study	1999–2010	Patients with CO intoxication versus control group	Increased long-term mortality (12 month follow-up period) after CO intoxication (8.39% versus 1.61% in control cohort)	441	Control cohort n = 8 820
Lee 2015 (16)	Population-based cohort study	2000–2011	Observational study, all patients with CO intoxication	Increased risk for cardiac arrhythmias (AHR 1.83; 95% CI [1.43; 2.33])	8 381	Control cohort n = 33 524
Kaya 2016 (18)	Prospective cohort study	2005–2007	Patients with CO intoxication, COHb at admission	10% of all patients with CO poisoning had a myocardial infarction during the follow-up period of 56 months on average; COHb concentrations >45% are a predictive parameter (with 98% sensitivity and 94.1% specificity) for developing myocardial infarction	1 013	No control group
Wong 2016 (11)	Population-based cohort study	2005–2010	Observational study, all patients with CO intoxication	CO intoxication: increased risk for dementia (AHR 2.75; 95% CI [2.26; 3.35])	14 590	Control cohort n = 58 360
Wong 2017 (15)	Population-based cohort study	2005–2010	Observational study, all patients with CO intoxication	CO intoxication: increased risk for cardiovascular events (AHR 2.0; 95% CI [1.83; 2.18])	13 939	Control cohort n = 55 756
Huang 2017 (19)	Population-based cohort study	1999–2012	Observational study, all patients with CO intoxication	CO intoxication: increased risk for diabetes mellitus (AHR 1.92; 95% CI [1.79; 2.06])	22 308	Control cohort n = 66 924

AHR, adjusted hazard ratio; atm, physical atmospheric pressure [standard atmosphere] (bar); 95% CI, 95% confidence interval; CO, carbon monoxide; COHb, carboxyhemoglobin; ECG, electrocardiogram; HBO, hyperbaric oxygen therapy

Clinical symptoms and long-term sequelae

The clinical symptoms of acute carbon monoxide intoxication range from headache and dizziness to loss of orientation, symptoms of cardiac angina, loss of consciousness, and death. They depend on the concentration and duration of exposure (7, 8). Detecting chronic poisoning with mild symptoms is often problematic (e8, e9), since the symptoms resemble those of influenza (e10).

In the long term, neurological injuries will manifest—for example, ataxias, dementia, concentration deficits, or abnormal behavior (2, 9–11, e11). Changes in subcortical structures and the pallidum, as well as hippocampal atrophy, have been observed (e12–e14). The severity of the initial intoxication did not necessarily correspond with the development of neuronal long term damage (e15, e16). Since long-term damage can manifest after an initially symptom-free interval ranging from days to weeks (9, 12) after the initial intoxication, a high estimated number of unreported cases has to be assumed (e17).

Patients with pre-existing coronary heart disease are exposed to a greater risk for myocardial infarction and arrhythmias (e18). A retrospective study

including 230 patients with CO poisoning described in 37% of cases raised cardiac biomarkers or changes on the electrocardiogram (13). In the prospective study of the same collective, 32 out of these 85 patients with myocardial involvement died during the median follow-up period of 7.6 years, whereas in the group without myocardial involvement only 22 of 145 patients died (adjusted hazard ratio 2.1; 95% CI [1.2; 3.7]; $P=0.009$). Age at the time of intoxication was an independent predictor of long-term mortality (AHR 1.2 for every additional five years in age; 95% CI [1.1; 1.3]; $P<0.001$) (14). Additional retrospective cohort studies showed an association between CO poisoning and the occurrence of severe cardiovascular events (AHR 2.00; 95% CI [1.83; 2.18]; or AHR 1.83; 95% CI [1.43; 2.33]) (15, 16). In case of comorbidities (diabetes mellitus, hypertension, hyperlipoproteinemia), the risk increased by a factor of 14.7 (95% CI [10.9; 19.9]) (16). *Table 1* shows a summarized overview of the studies.

Method

For this review article, we conducted a search according to existing guidelines in the guideline databases

TABLE 2

Contents and levels of evidence of identified recommendations and guidelines

First author (year) title	Publication type	Recommendation	Reported methodological quality	Reported recommendation grade	Level of evidence (LoE ^{*1})
Buckley (2011): Hyperbaric oxygen for carbon monoxide poisoning (21)	Systematic review (Cochrane review)	– 100% oxygen or HBOT; no recommendation of routine HBOT if proof of superiority is lacking	Systematic search and review, structured consensus finding	Very low (according to GRADE quality of evidence ^{*2})	1a
Mintegi (2013): Pediatric cyanide poisoning by fire smoke inhalation (22)	Recommended course of action from an expert group	– 100% oxygen	Consensus finding (informal approach)	(–)	(–)
Truhlář (2015): Circulatory arrest in specific situations (23)	Evidence and consensus based guideline from a representative committee	– 100% oxygen – HBOT in pregnancy or cardiac ischemia	Systematic search and review, structured consensus finding	High	2b
Wolf (2017): Clinical policy: critical issues in the evaluation and management of [...] with acute carbon monoxide poisoning (20)	Evidence and consensus based guideline from a representative committee	– NBOT or HBOT (no recommendation) – Diagnostic evaluation: ECG and cardiac enzymes, no routine use of non-invasive COHb measurements	Systematic search and review, structured consensus finding	Moderate	2b
Mathieu (2017): [...] recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment (24)	Evidence and consensus based guideline from a representative committee	– 100% oxygen – HBOT within up to 24 hours after exposure	Systematic search and review, structured consensus finding	High	(2–3)

^{*1} Evidence review according to the Levels of Evidence (LoE) of the Oxford Centre for Evidence-Based Medicine of 2009 (e26)

^{*2} GRADE (Grading of Recommendations Assessment, Development and Evaluation) quality of evidence:

High Further research is very unlikely to change our confidence in the estimate of effect.

Moderate Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low Any estimate of effect is very uncertain.

COHb, carboxyhemoglobin; ECG, electrocardiogram; HBOT, hyperbaric oxygen therapy; NBOT, normobaric oxygen therapy

AWMF [Association of the Scientific Medical Societies in Germany] (e19), NCG [National Guideline Clearinghouse] (e20), and GIN [Guidelines International Network] (e21).

For an evidence-based assessment we conducted a selective literature search in the databases Medline (accessed via PubMed [e22]) and the Cochrane Database (e23) (eBox).

Diagnosis and therapy

Therapeutic recommendations as per the included reference guidelines

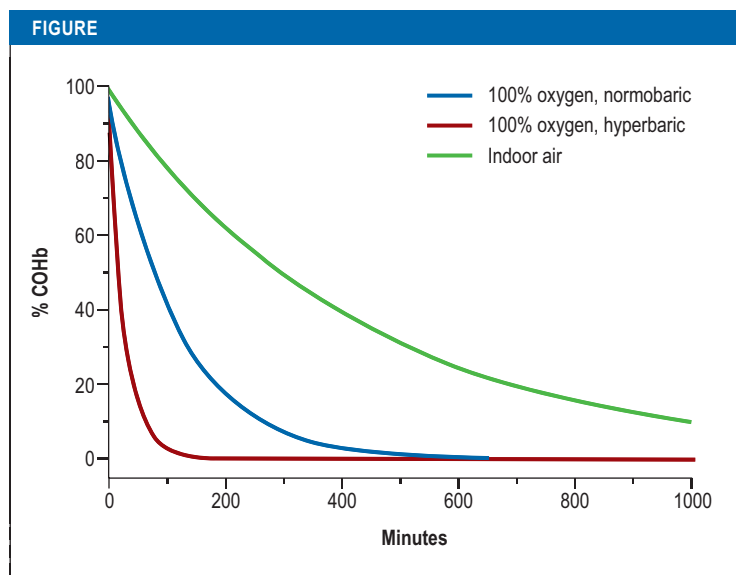
The description of the therapeutic recommendations in patients with CO poisoning was undertaken in accordance with the German Instrument for Methodological Guideline Appraisal [Deutsches Leitlinien-Bewertungsinstrument, DELBI] (e24). We checked for methodological quality, level of evidence, and grade of recommendation (e25). We based our appraisal of the evidence of the Oxford scheme (e26) (Table 2).

Preclinical phase

Administration of 100% oxygen as early as possible is recommended for all patients with a relevant suspected diagnosis (in alert patients, for example, by means of non-invasive continuous airway pressure (CPAP), or respiration using a mask with a demand valve, or ad-

ministration of 15 L/min O₂ through a reservoir mask) (20, 21–24). In suspected CO poisoning, an early diagnosis has a crucial role in initiating targeted and timely treatment. In principle, the diagnosis of CO poisoning is based on clinical symptoms and suspected or confirmed exposure (25). For the purposes of verification, carboxyhemoglobin (COHb) should be measured in a blood gas analysis (BGA) (20). Preclinically, a validated spectral photometric method of BGA is mostly not available. Normal pulse oximeters are not suitable for distinguishing between COHb and oxyhemoglobin (e27, e28), whereas 8-wave pulse oximeters enable detection (e29, e30). However, precision has been reported to be poor (e31), and no recommendation for their standard use has been issued by the American College of Emergency Physicians (20). Since the COHb measurement is only one concern when assessing the overall clinical symptoms, the authors still deem pulse oximetry to be a useful—and low-cost (e32)—orientation tool in the emergency rescue setting.

Confirmation of COHb does not differ to a clinically relevant degree in arterial and venous specimens (e33, e34). In order to evaluate the acid-base status, however, arterial measurement should be the method of choice. Hampson et al. showed on the basis of a database analysis of 1505 patients that with an initial



Decrease in carboxyhemoglobin (COHb) under different therapeutic conditions (2). half-life for indoor air (320 min), 100% normobaric oxygen respiration (74 min), and 100% hyperbaric oxygen respiration at 3.0 bar (20 min) (reproduced with permission from the American Thoracic Society)

pH value <7.2 , mortality increased by up to 50%, independently of COHb (26). If concomitant cardiac symptoms occur, a 12-lead ECG should be conducted and cardiological biomarkers determined (20). Generally, the type of exposure to CO (e35), as well as exposure time and exposure level (7), will affect the severity of clinical symptoms. The mere CO measurement correlates poorly with the severity of the clinical manifestation (8, 26). What is important is therefore the overall clinical picture, not the individual measurement. An exact history should consist of type and duration of exposure, initial main symptoms (syncope, confusion, hypoxia, chest tightness, arrhythmias), more unspecific neurological symptoms (headache, nausea, impaired vigilance), and a possible pregnancy should be checked for.

Elimination

The supreme objective is the elimination of carbon monoxide from the organism, in order to avert acute and long-term sequelae. The treatment should be continued until the COHb measurement has dropped to normal values ($<3\%$) and the patient is free from symptoms (25). After exposure to fumes, and in addition to CO, additive cyanide poisoning should also be considered, whose effects will develop within minutes (4, 22, e36). Poison information centers in Germany therefore recommend that in case of severe intoxication owing to smoke inhalation, combined intoxication with CO and cyanides should be considered and a cyanide antidote should be given that has few adverse effects—such as hydroxocobalamin (e37). Administration of hydroxocobalamin can, however, seriously hamper the precision of a blood gas analysis for CO

(e38–e41). By contrast to the cyanide antidote, no established pharmacological concept exists for CO, even though some animal studies have shown promising approaches (2, e42–e46).

The higher the provided partial pressure of oxygen (pO_2), the quicker the CO will be eliminated. The elimination half life of CO after respiration of indoor air is about 320 minutes and can be reduced to 74 ± 25 minutes by treating patients with 100% oxygen (e47). Treatment with hyperbaric oxygen ($pO_2 = 2.5\text{bar}$) lowered the half life to about 20 minutes (e48, e49). The fivefold half life that is required for complete elimination is about 370 minutes for treatment with normobaric 100% oxygen (Figure). Some animal studies have shown that using hyperbaric oxygen restricts inflammatory processes, mitochondrial dysfunction, and lipid peroxidation (e50–e56). Recent clinical studies (Table 2) have also focused on late sequelae of CO intoxication, such as dementia, diabetes mellitus, cardiovascular events, and raised long-term mortality (11, 13–15, 19). Being older than 36 years (odds ratio [OR]: 2.6; 95% CI [1.3; 4.9]) and an exposure period of longer than 24 hours (OR: 2.0; 95% CI [1.0; 3.8]; $P=0.046$) are considered risk factors for developing neuronal late sequelae (27).

Because the studies available so far are subject to great heterogeneity, no clear, generally accepted recommendation exists for what should be done (Table 3). No controlled randomized multicenter study with defined exclusion and inclusion criteria, defined treatment algorithms, and an adequate follow-up protocol has been conducted so far (20).

Assessment of hyperbaric oxygen therapy versus normobaric oxygen therapy

The intracellular and extracellular effects of carbon monoxide poisoning affect in particular the organs without oxygen reserves (heart, brain). Toxicologically, the quickest possible elimination of the poison is the most sensible way to prevent further injury. The higher the partial pressure of oxygen provided, the shorter the elimination period—which would in theory support hyperbaric oxygen therapy (HBOT). In practice, however, HBOT is the subject of controversial discussion (20, 21). Critics point out the great logistical challenges and lacking evidence. In actual fact, the heterogeneity of the studies to date (in terms of study design, kind of exposure, severity of intoxication, delay in treatment, treatment pressures applied, and follow-up period) barely allows for any evidence-based recommendation regarding the type and extent of HBOT (25). What adds to the dilemma is the fact that the HBOT therapy schemes applied vary widely across Europe (e57), which imposes limitations on future meta-analyses and their validity too.

The study evidence for the benefit of HBOT in adults with regard to neurological sequelae subsequent to CO poisoning is inconclusive. An older randomized study found no benefit for HBOT after one month in 629 patients with acute CO intoxication

(2 standard atmospheres [atm]) (28). A randomized controlled double blinded trial (31) including 191 patients showed no difference after one month, irrespective of the selected treatment pattern (2.8 atm versus NBOT). What is of note, however, is the fact that the proportion of patients seen at follow-up was low, at 46%. Annane et al. (32) randomized 385 patients to two study arms. HBOT (2 atm) was not found to confer any benefit in terms of cognitive performance compared with NBOT; rather, repeated HBOT tendentially yielded worse outcomes. These three studies included patients whose therapy was started within 12 hours of CO exposure.

In contrast, a non-blinded prospective randomized trial reported by Thom et al. found fewer delayed neurological symptoms after HBOT, independently of the initial extent and clinical symptoms of the intoxication. Neurological testing also yielded better results for the HBOT group after one month (36). Weaver et al. evaluated in a prospective randomized double blinded study the long term course after HBOT (3 atm). They found a benefit for HBOT in cognitive outcomes after six and 12 months (10). However, Weaver et al. named as their study objective the target parameter of delayed neurological deficit, yet what they actually showed was rates of persistent neurological deficit (10). Furthermore, the study was stopped early when a benefit advantage emerged for HBOT (e58).

A 2011 Cochrane review critically discussed the studies available up to that date. The authors concluded in their meta-analysis that the benefit of HBOT versus normobaric oxygen treatment is not confirmed (OR 0.78; 95% CI [0.54; 1.12]). However, the conclusion is qualified by the heterogeneity of the available studies (21). No further larger prospective studies have been published since then.

Recent retrospective database analyses have shown the importance of HBOT in particular with regard to preventing long-term sequelae. A study by Rose et al. showed that using HBOT reduced acute case fatality as well as case fatality after one year (36). Huang et al. in a retrospective analysis of more than 25 000 cases of CO poisoning also showed a benefit for HBOT in terms of mortality at four years (34). However, the treatment was not found to have any effect on late neurological sequelae.

In these analyses, confounding variables with a risk of bias are especially the heterogeneous therapeutic schemes for HBOT and the fact that the study by Huang et al. does not provide any information of the severity of the intoxication. It is possible that the most severely intoxicated patients were not given HBOT. Still, the large number of cases of CO poisoning underlines the importance of such patients in clinical practice. The large amount of late sequelae and raised long-term mortality also give cause for alarm (11, 13–15, 17, 19) (Table 1). It remains to be seen whether prospective studies will in future allow for a profound reassessment of HBOT. A recent prospec-

BOX 1

Treating carbon monoxide poisoning

- Respiration using 100% oxygen in suspected carbon monoxide poisoning (20, 22, 23, 40).
- Diagnosis of carbon monoxide poisoning on the basis of relevant symptoms and raised COHb concentrations on blood gas analysis (20)
- Continue giving 100% oxygen until symptoms resolve or carbon monoxide intoxication is no longer detectable (20, 23, 24)
- Patients with CO poisoning should continue to be treated according to the standards of emergency medicine.
- The decision in favor of hyperbaric oxygen therapy should be made if a patient with carbon monoxide poisoning presents with impaired consciousness, cardiac ischemia, neurological deficits, pregnancy, or very high COHb concentrations (23, 24)
- In patients with severe carbon monoxide poisoning, an ECG and a biomarker analysis for cardiac ischemia should be undertaken (20).
- If hyperbaric oxygen therapy is given this should be started within six hours (20), but under no circumstances after more than 24 hours (24).
- Patients should be examined for cognitive sequelae 4–6 weeks after carbon monoxide poisoning (22).

CO, carbon monoxide; COHb, carboxyhemoglobin; ECG, electrocardiogram

tive study is about to conclude (ClinicalTrials.gov, registration number NCT00465855).

Pregnant women and children

No randomized trials in pregnant women exist; recommendations are based on theoretical studies (e59), animal experiments (e60), and analyses from trauma care (e61). It seems that in the fetal system, saturation as well as elimination occur slower than in the maternal system. Especially in case of longer exposures, fetal COHb measurements may even exceed maternal levels (e62). A case report showed a COHb measurement of 61% at fetal autopsy, although the mother had a measurement of 7% after just an hour's O₂ treatment. For this reason, some authors regard pregnancy as a strict indication for HBOT (23), especially in the presence of neurological symptoms, signs of fetal stress, occurrence of syncope, or high COHb levels (4).

Because of small case numbers, assessing and making recommendations for hyperbaric oxygen therapy in children is possible to a limited degree only in the studies published to date. In the studies reported by Meert et al. (0.1–14.9 years, median 3.5 years) (37) and Chou et al. (0–18 years, median 7.2 years) (38), smoke inhalation often resulted in circulatory arrest; this was barely seen in pure CO intoxication. Neither of the two studies showed a benefit for HBOT versus NBOT. In a retrospective analysis by Chang et al. (33), fire fumes were excluded as a potential confounder (0.1–12.2 years, median 6.2 years); no

TABLE 3

Existing evidence for therapy using hyperbaric oxygen versus normobaric oxygen

First author/ year	Design	Intervention/ variable	Primary endpoint	Result	N	Benefit advan- tage for HBO	Comment
Raphael 1989 (28)	Randomized, HBO in loss of con- sciousness	HBO (2.0 atm) vs 6 h NBO, in unconscious patients: 1 × HBO vs 2 × HBO (2 atm)	Neurological symptoms after 1 month	No difference in symptoms after 1 month	629	No	No loss of conscious- ness: n = 170 vs. n = 173; loss of consciousness: n = 141 vs. n = 145
Ducasse 1995 (29)	Randomized controlled	HBO (2.5 atm) vs NBO	Clinical impairments	Decreased reactivity of cerebral blood flow on acetazolamide and additional EEG changes after NBO; additional clinical impairments after NBO	26	Yes	n = 13 vs n = 13
Thom 2009 (30)	Randomized, no patients with loss of con- sciousness	HBO (2.8 atm and 2.0 atm) vs NBO	Neurological late sequelae	Fewer neurological impairments after HBO	65	Yes	n = 33 HBO, n = 32 NBO
Schein- kestel 1999 (31)	Double blinded, randomized controlled trial	3 courses of HBO (2.8 atm) vs 3 placebo courses of NBO	Neurological symptoms at discharge, symptoms after discharge	No difference in neurological sequelae at/after discharge	191	No	n = 104 HBO, n = 87 NBO, patients in hyperbaric chambers without increased pressure as placebo treatment
Weaver 2002 (10)	Double blinded, randomized controlled trial	3 courses of HBO (3 atm, then 2 atm) vs 3 placebo courses of NBO	Cognitive se- quelae after 6 weeks	Fewer cognitive sequelae with HBO after 6 and 12 months	150	Yes	n = 104 HBO, n = 87 NBO, patients in hyperbaric chambers without increased pressure as placebo treatment
Weaver 2007 (27)	Retrospective analysis/ post-hoc analysis	Patients from randomized study and excluded pa- tients with CO intoxication	Cognitive se- quelae after 6 weeks	Benefit advantage of HBO in patients >36 years or CO exposure >24 h; benefit of HBO in patients with loss of consciousness or high COHb values	238	Yes	Patients partly from Weaver 2002 (10), n = 75 with HBO, n = 163 without HBO
Annan 2011 (32)	Randomized controlled	Study had two arms, di- vided by symptoms: - transient loss of con- sciousness: NBO and HBO (2 atm) vs NBO - initial coma: NBO and 2 courses of HBO (2 atm) vs NBO und 1 course of HBO (2 atm)	Complete recovery after 1 month	Complete recovery after 1 month, no difference	385	No	Temporary loss of consciousness: n = 93 HBO vs n = 86 NBO Initial coma: n = 105 NBO and 2 × HBO, n = 101 NBO, and 1 × HBO
Chang 2016 (33)	Retrospective cohort study	Children with HBO vs NBO	Neurological late sequelae	No benefit of HBO	81	No	n = 21 HBO, n = 60 NBO, precise treatment modalities not known
Huang 2017 (34)	Retrospective cohort study	HBO vs no HBO	Neurological sequelae, fatality	Lower mortality with HBO especially in patients with <20 years of life and patients with pulmonary failure (4 years of follow-up); no reduction in neurological late sequelae for HBO; more frequent treatment (>2 courses) is better than one course	25 737	Yes	n = 7 278 HBO therapy, n = 18 459 no HBO, precise treat- ment modalities not known
Rose 2018 (35)	Retrospective analysis	HBO vs no HBO	Fatality; fatality at 1 year	Reduced acute fatality and fatality at 1 year with HBO	1 099	Yes	n = 285 HBO, n = 811 no HBO, precise treatment modalities not known

atm, physical atmospheric pressure [standard atmosphere] (bar); CO, carbon monoxide; COHb, carboxyhemoglobin; EEG, electroencephalogram; HBO, hyperbaric oxygen therapy; NBO, normobaric oxygen therapy

benefit advantage was found for HBOT in terms of preventing neurological deficits. However, it should be borne in mind that the initial COHb was significantly higher in the HBOT group (27.4 ± 7.3 versus 17.6 ± 6.3). These negative results are contrasted by a recently published, large retrospective cohort analysis, which showed reduced fatality after HBOT especially in patients younger than 20 years (34) (Table 3). In parallel to adults, children (0–18 years, median 11 years) with severe CO poisoning also had raised troponin T concentrations (39).

Conclusion

In sum, on the basis of the randomized controlled trials published to date, no superiority can be confirmed for HBOT over normobaric oxygen therapy. The latest publications were of retrospective database evaluations that showed greater benefits for HBOT in terms of neurological outcomes and long-term survival. A guideline for the treatment of CO intoxication is currently in development (AWMF registration number 040–012) and aims to standardize relevant healthcare in Germany. On this background, HBOT should be the method of choice in adult patients with neurological deficits, cardiac ischemias, loss of consciousness, metabolic acidosis, and COHb values $>25\%$. Regardless of these inclusion criteria, any decision to treat is always an individual decision. Every patient with clinical symptoms of CO intoxication should be treated with high oxygen partial pressures until the COHb concentration has dropped to $\leq 3\%$ or clinical symptoms have resolved completely (25).

Conflict of interest statement

Dr Eichhorn and Prof Jüttner are board members of the German Diving and Hyperbaric Medical Society.

Prof Jüttner is the spokesperson of the section for hyperbaric medicine of the German Interdisciplinary Association of Intensive Care and Emergency Medicine (DIVI).

Dr Thudium declares that no conflict of interest exists.

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Key messages

- The symptoms of carbon monoxide poisoning are usually non-specific. In patients with unclear neurological symptoms and possible exposure, carbon monoxide should be urgently considered as a differential diagnosis.
- The treatment aims in particular to prevent long-term harms, such as cortical dysfunction, Parkinson's syndrome, Parkinson's disease, dementia, cardiac complications, as well as reduce mortality in the long term.
- All patients with symptomatic carbon monoxide poisoning should be treated with 100% oxygen as soon as possible.
- In severe cases of fire fume intoxication, combined poisoning with CO and cyanides should be considered.
- The evidence for the benefit advantage of hyperbaric oxygen is weak in view of the heterogeneity of the available studies. The decision in favor of HBOT seems sensible in severe CO intoxication or in pregnant women.

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► **Supplementary material**

For eReferences please refer to:
www.aerzteblatt-international.de/ref5118

eTable, eBox:
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Supplementary material to:

The Diagnosis and Treatment of Carbon Monoxide Poisoning

by Lars Eichhorn, Marcus Thudium, and Björn Jüttner

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eTABLE

Cases of carbon monoxide poisoning in Germany (ICD 10: T58, inpatients) (e63)

	2007		2010	2011	2012	2013	2014	2015	2016
Absolute case numbers	3943	[...]	4171	3914	4302	3960	3764	3481	3611
Deaths	282		481	494	582	514	594	648	–

eBOX

Search strategy

Medical Literature Analysis and Retrieval System Online (MEDLINE, accessed via PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), and Health Technology Assessment Database (HTA)

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF, Association of the Scientific Medical Societies in Germany), National Guideline Clearinghouse (NGC), and Guidelines International Library (GIN)

Search date 18 September 2018

PubMed (→ 159 hits):

("carbon monoxide poisoning"[MeSH terms] OR ("carbon"[All Fields] AND "monoxide"[all fields] AND "poisoning"[all fields]) OR "carbon monoxide poisoning"[all fields]) AND (randomized controlled trial[ptyp] OR practice guideline[ptyp] OR systematic[sb] OR clinical trial[ptyp] OR multicenter study[ptyp] OR observational study[ptyp] OR controlled clinical trial[ptyp] OR guideline[ptyp] OR validation studies[ptyp] OR meta-analysis[ptyp])

CENTRAL (→ 82 hits):

Carbon monoxide poisoning in title, abstract, keywords in trials

CDSR (→ 1 hits):

Carbon monoxide poisoning in title, abstract, keywords in Cochrane reviews

DARE (→ 3 hits):

Carbon monoxide poisoning in title, abstract, keywords in other reviews

HTA (→ 7 hits):

Carbon monoxide poisoning in title, abstract, keywords in technology assessments

AWMF (→ 18 hits):

Kohlenmonoxid

NGC (→ 2 hits):

Carbon monoxide poisoning

GIN (→ 2 hits):

Carbon monoxide poisoning