Risk factors for short-term mortality from carbon monoxide poisoning treated with hyperbaric oxygen*

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. List the causes of carbon monoxide poisoning.
2. Describe factors influencing mortality after carbon monoxide poisoning.
3. Use this information in a clinical setting.

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Objective: **Carbon monoxide (CO) poisoning is common in the United States, accounting for approximately 2,700 deaths annually. Few publications have described the mortality rate of CO-poisoned patients who survive to reach a hospital and die despite maximal medical care. Further, while risk factors for cognitive sequelae in survivors of CO poisoning have become clearer recently, factors associated with death are less well defined. This study was conducted to 1) determine the short-term mortality risk for patients treated with hyperbaric oxygen for CO poisoning, and 2) determine whether any factors related to the poisoning episode are predictive of mortality.**

Design/Setting/Patients: **A departmental database and medical records of 1,505 consecutive patients treated with hyperbaric oxygen at a single institution from 1978 to 2005 were reviewed.**

Measurements: **Demographic and clinical data were extracted for analysis. Mortality data, including cause of death, were obtained through a search of the National Death Index of the National Center for Health Statistics.**

Main Results: **A total of 38 patients experienced short-term mortality from their episode of CO poisoning, yielding a death rate of 2.6% in medically treated patients. Characteristics significantly associated with mortality included fire as a source of CO, loss of consciousness, carboxyhemoglobin level, arterial pH, and presence of endotracheal intubation during hyperbaric treatment.**

Conclusions: **The mortality rate for medically treated CO-poisoned patients in this series was 2.6%, similar to the limited combined experience previously reported in the literature. Factors most strongly associated with mortality were severe metabolic acidosis and need for endotracheal intubation. (Crit Care Med 2008; 36:2523–2527)**

KEY WORDS: carbon monoxide; poisoning; mortality; cause of death; hyperbaric oxygen

Carbon monoxide (CO) poisoning is common in the United States, accounting for an estimated 50,000 emergency department visits annually (1). It is one of the leading causes of poisoning deaths, responsible for approximately 2,700 fatalities annually, according to the Centers for Disease Control and Prevention (2).

Such epidemiologic tabulations of deaths from CO poisoning use death certificate codes for cause of death, searching for and counting those that represent CO poisoning. They include both individuals who die in the field prehospital, as well as those who survive to treatment at a medical facility and die shortly thereafter despite supportive therapy. A recent report by Henry et al. (3) noted that very few case series of CO poisoning have described short-term mortality among patients who are treated in a hospital. As such, the death rate from medically

***See also p. 2684.**

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Supported, in part, by the Edward H. Morgan Chair in Pulmonary and Critical Care Medicine of Virginia Mason Medical Center.

The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e31818419d8

treated CO poisoning is believed to be poorly defined.

The present study was undertaken to investigate the issues of short-term mortality in a large population of CO-poisoned patients treated at one medical center over three decades. We sought 1) to determine the short-term mortality risk for patients treated with hyperbaric oxygen for acute CO poisoning, and 2) to determine whether any factors related to the poisoning episode were associated with short-term mortality.

MATERIALS AND METHODS

Following approval by the Institutional Review Board of Virginia Mason Medical Center in Seattle, WA, patients treated for CO poisoning with hyperbaric oxygen (HBO_2) therapy at the Virginia Mason Medical Center for Hyperbaric Medicine from May 1978 through December 2005 were reviewed. They were identified and basic information obtained about each through use of an institutionally approved database containing all patients treated in the facility. Additional information was extracted when necessary from the patients' medical records available at our institution.

Although guidelines for hyperbaric treatment of CO-poisoned patients evolved over the years encompassed by this study, in general patients were accepted for HBO_2 therapy if they manifested transient or prolonged unconsciousness, abnormal neurologic findings on physical examination, evidence of cardiac ischemia, or carboxyhemoglobin (COHb) level $>$ 25% to 30%. Similarly, the hyperbaric treatment protocol utilized for CO poisoning changed over three decades. From May 1978 to July 1986, the U.S. Navy Treatment Table 6 protocol was used (Protocol 1), administering 240 total minutes of 100% oxygen at a maximum pressure of 2.8 atmospheres absolute (atm abs). From July 1986 to February 1992, a protocol delivering 92 mins of oxygen at 2.8 atm abs was used (Protocol 2). Since February 1992, the U.S. Air Force CO protocol has been used, administering 96 total minutes of oxygen at a maximum pressure of 3.0 atm abs (Protocol 3). In almost all cases, a single hyperbaric treatment was administered. Only in rare instances were some patients with persistent neurologic signs retreated.

Demographic data including first and last name, middle initial, date of birth (DOB), social security number (SSN), gender, race/ethnicity, intent and source of poisoning, and date of treatment were compiled from the database and medical records as available. In addition, clinical data including COHb level, arterial pH, history of loss of consciousness (level of consciousness), and presence of endotracheal intubation at the time of hyperbaric treatment were extracted.

An application was then submitted to the National Center for Health Statistics of the Center for Disease Control and Prevention to query the National Death Index (NDI) to obtain mortality information about the patients. The NDI is a central computerized index of death record information on file in State vital statistics offices (4). It is available to investigators only for statistical purposes in medical and health research. In addition to obtaining date and location of death from the NDI, investigators can also obtain cause of death codes using the NDI Plus service. Following approval of an NDI Plus application by the National Centers for Health Statistics, a space-delimited text file containing the patients' demographic information including first and last name, middle initial, SSN, DOB, gender, and race was submitted according to NDI protocol. NDI search criteria specify that each patient record must contain at least one of the following combinations of data items: 1) first and last name and SSN, 2) first and last name and month and year of birth, 3) SSN and date of birth and gender. Patients for whom neither SSN nor DOB could be obtained were excluded from the study due to an inability to search for their death information according to NDI criteria. By mid-2007, search results were only available for the years 1979 through 2005, limiting analysis to patients who had been treated through 2005.

The mortality information obtained from the NDI Plus search was used to identify individuals who died as a direct result of the acute poisoning episode. All deaths occurring within 90 days of the date of treatment were reviewed in detail. Cause of death for these individuals, as obtained from the NDI Plus search, was used to determine whether they died from a cause directly related to the acute poisoning event or from an unrelated cause.

For individuals suffering short-term mortality because of CO poisoning, corresponding demographic and clinical information was examined to determine whether any factors could be identified that were predictive. Analysis included use of two-tailed Fisher's exact test, two-tailed t test, linear regression, and stepwise logistic regression.

RESULTS

A total of 1,505 patients were treated with HBO_2 for acute CO poisoning from May 1978 through December 2005. Of those, 32 patients were excluded from analysis because their records contained insufficient demographic information to submit for an NDI search, leaving 1,473 patients from which the data reported were obtained. This included 961 males (65%) and 512 females (35%) ranging in age from 0 yrs to 92 yrs, and averaging 35 $\pm$ 19 yrs (mean $\pm$ SD) (median 33 yrs). The CO exposure was accidental in 1,024 patients (70%), intentional in 441 cases (30%), and indeterminate in 8 patients (1%).

NDI Plus data and records review indicated that 50 individuals (3.4%) had died within 90 days of their poisoning episode. Causes of death occurring out to 90 days after hyperbaric treatment were reviewed to ensure that all deaths directly related to the event were identified. Of them, 38 (2.6%) were consistent with being directly related to the acute poisoning event and were described as motor vehicle exhaust inhalation (12), smoke inhalation (11), fire (6), CO poisoning (6), burns (2), and intracranial hemorrhage occurring 1 day after severe poisoning (1). Deaths coded as suicide by handgun (5), suicide by motor vehicle accident (1), motor vehicle accident (1), cirrhosis (1), tongue cancer (1), drug overdose of unknown intent (1), atherosclerotic heart disease (1), and alcoholism (1) were excluded. The six suicidal deaths were not believed to be related to CO-induced mood disorders as all occurred in individuals who suffered intentional CO poisoning initially.

Of the 1,473 patients studied, 216 (15%) were treated with hyperbaric Protocol 1, 398 (27%) Protocol 2 and 859 (58%) Protocol 3 (protocol details described in Methods). Among the 38 dying from the acute poisoning episode, 8 (21%), 12 (32%), and 18 (47%) were treated with each of the protocols. Of the 38 decedents, 30 (79%) received one hyperbaric treatment and eight (21%) received two.

Individuals died 0 to 59 days following poisoning (median 2 days). Sources of CO among those who died included fires (20), motor vehicles (14), butane heater (1), furnace (1), gasoline powered electrical generator (1), and wood burning stove (1).

Demographic and clinical characteristics of the nonsurvivors and survivors are detailed in Table 1. Variables significantly different (p value <0.01) by univariate analysis between those who died and survived included fire as a source of CO, loss of consciousness, COHb level, arterial pH, and presence of endotracheal intubation during hyperbaric treatment. Subsequent stepwise logistic regression demonstrated that arterial pH ($p < 0.0001$) and presence of endotracheal intubation ($p = 0.002$) were statistically significant predictors of death. It is noted that over 40% of records were missing arterial pH measurements and were therefore excluded from analysis.

Table 1. Demographic and clinical characteristics of individuals who died of acute carbon monoxide (CO) poisoning, as compared with survivors

	Nonsurvivors (n = 38)	Survivors (n = 1435)	*p* Univariate Analysis	*p* Logistic Regression
Gender	53% male	66% male	0.12	NS
Intent of poisoning				
Accidental	70%	70%	1.0000	NS
Intentional	30%	30%		
Source of CO				
Fire	53%	11%	<0.0001	NS
Nonfire	47%	89%		
Loss of consciousness	100%	52%	<0.0001	NS
COHb%	31.1 ± 13.5	22.6 ± 11.2	<0.0001	NS
Initial arterial pH	7.20 ± 0.15	7.39 ± 0.10	<0.0001	<0.0001
Intubation during HBO_2	76%	16%	<0.0001	0.002

COHb, carboxyhemoglobin; HBO_2, hyperbaric oxygen.

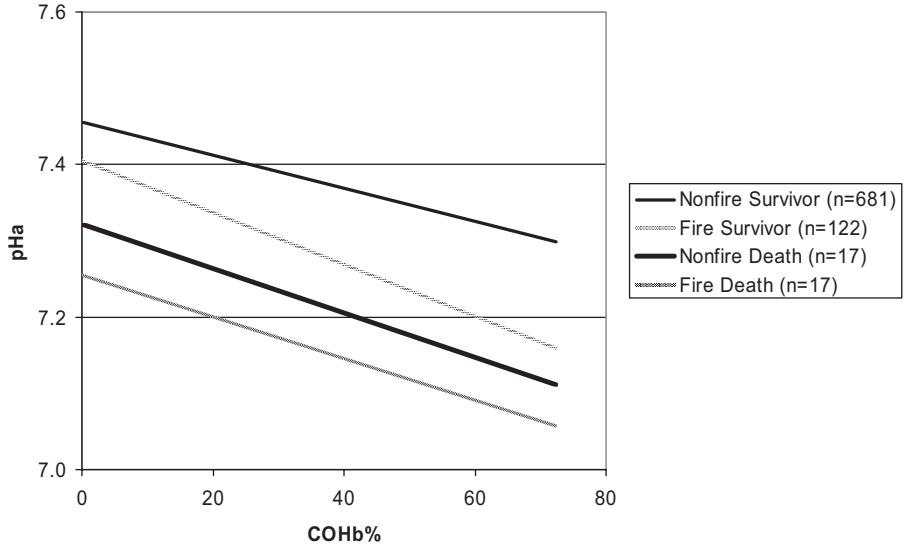

Figure 1. Initial arterial pH values vs. initial carboxyhemoglobin (*COHb*) levels among the 837 patients for whom both measurements were available. Equations for the linear regression lines shown are listed in the Results section.

Of the 20 patients who died following CO exposure from a fire, eight had concomitant burn injuries. Among them, body surface area (BSA) involvement averaged 18 ± 20%. Three patients had BSA involvement or 20% or greater (20%, 34%, and 60%). Records available for review described abnormalities of the pulmonary parenchyma on chest radiograph in 7 of 14 decedents exposed from fire. Because most were transferred to the regional trauma hospital for posthyperbaric care, the incidence of subsequent significant lung injury is not known.

Figure 1 compares initial arterial pH with COHb levels in the 837 patients for whom both measurements were available. The linear regression equation for the 681 patients exposed to CO from a nonfire source and surviving was $y = -0.0022x + 7.46$, $R^2 = 0.0809$ ($p < 0.0001$), for 122 exposed from a fire and surviving $y = -0.0034x + 7.41$, $R^2 = 0.1086$ ($p = 0.0002$), for 17 exposed from a nonfire source and dying $y = -0.0037x + 7.35$, $R^2 = 0.1166$ ($p = 0.18$), and 17 exposed from a fire and dying $y = -0.0027x + 7.26$, $R^2 = 0.0570$ ($p = 0.36$).

Figures 2*a* and 2*b* compare mortality rates to initial carboxyhemoglobin levels and initial arterial pH values, respectively. More patients in the study had COHb measured (n = 1435) than pHa (n = 846).

Arterial blood gas results were available for 17 of the 20 patients who died following CO exposure from fire. Of them, arterial $Paco_2$ averaged mean 32 ± 13 mm Hg and was less than 45 mm Hg in 14, consistent with primary metabolic acidosis. In the remaining three patients, acid–base status was consistent with combined metabolic and respiratory acidosis (pHa/$Paco_2$ combinations of 6.98/64, 6.90/68, 7.22/50).

DISCUSSION

The present study describes the largest series of patients with carbon monoxide poisoning treated with hyperbaric oxygen reported in the English literature to date and demonstrates a short-term mortality rate because of the poisoning of 2.6%. Eight other published series describing at least 100 CO-poisoned patients treated with HBO_2 and reporting mortality from CO poisoning are listed in Table 2. Their combined death rate was 3.9% among 2,359 patients. Adding the present series (and subtracting the patients reported in Reference 8 because they are included herein) yields a short-term death rate of 3.1% among 3,832 patients receiving medical treatment for acute CO poisoning in large series. Because there are an estimated 50,000 emergency department visits for CO poisoning in the United States annually (1), a mortality rate of 3.1% implies approximately 1,550 deaths in the country despite hospital-based medical care.

When looking at the studies listed in Table 2, it is difficult to draw any conclusions regarding differences in mortality from CO poisoning related to the therapy administered (normobaric vs. hyperbaric oxygen). In fact, with death being such an infrequent outcome in medically treated patients, it would require a multicentered trial of enormous proportions to determine whether there is a survival advantage related to treatment.

Because of this, randomized studies to date have used neurologic sequelae as the outcome measure when examining different treatments. Neurologic sequelae are much more common than death in CO-poisoned patients. In the study by Weaver et al. (13), 18% of patients with hyperbaric oxygen manifest cognitive sequelae at 1 yr after poisoning, when compared with 33% of patients treated with normobaric oxygen. A recent expert panel report addressing unresolved issues in the treatment of CO poisoning focused on delay to treatment, number of hyperbaric treatments administered, and the specifics of the hyperbaric protocol, all with regard to neurologic outcome and not mortality (14).

It is likely that medical treatment has only a very small mortality benefit in the CO-poisoned patient. This is suggested by the fact that mortality rates are so similar across time and treatments, despite divergent patient populations (Table 2). Furthermore, some patients may experience unsurvivable insults, as was suggested in our earlier report describing 18 consecutive deaths among patients treated with hyperbaric oxygen following resuscitation from CO-related cardiac arrest (15).

Factors found by logistic regression to correlate with risk for death in the present study included arterial blood pH and presence of endotracheal intubation. In the large study by Goulon et al. (5), it was noted that mortality of CO-poisoned patients was related to the severity of metabolic acidosis. They described stepwise increases in the mortality rate as arterial pH dropped from the range greater than 7.35 to 7.35–7.25 and then to less than 7.25. Using those same categories in the present study, a similar result is seen with mortality rates of 1%, 3%, and 30% for those ranges, respectively.

Although need for endotracheal intubation and low arterial pH may simply represent severity of CO poisoning, severe systemic acidosis could be an indicator of another process. CO causes metabolic acidosis by interfering with systemic oxygen transport (COHb formation), as well as by impairing intracellular energy metabolism. It can also cause secondary impairment of oxygen delivery by reducing cardiac output because CO poisoning is known to cause myocardial injury and dysfunction (12). Figure 1 illustrates arterial pH as a function of COHb level in various subgroups of patients in this series. Regression lines drawn on Figure 1 demonstrate that the average arterial pH is lower in nonsurvivors than survivors, irregardless of CO source. One might speculate that nonsurvivors have some propensity for systemic acidosis, such as baseline anemia or cardiac dysfunction.

It should be noted that those exposed to CO from a fire source have lower arterial pH than those exposed by nonfire CO sources, both among survivors and nonsurvivors (Fig. 1). Fire was a much more common CO source among those who died. In conjunction with lower arterial pH, the possibility of concomitant cyanide poisoning should be considered. In burn victims without serious burns, elevation of plasma lactate has been shown to be a sensitive and specific indicator of cyanide intoxication (16). Unfortunately, neither cyanide nor lactate levels were present in the available records of patients in the current series. One patient who died following CO exposure from a fire was also treated for cyanide poisoning.

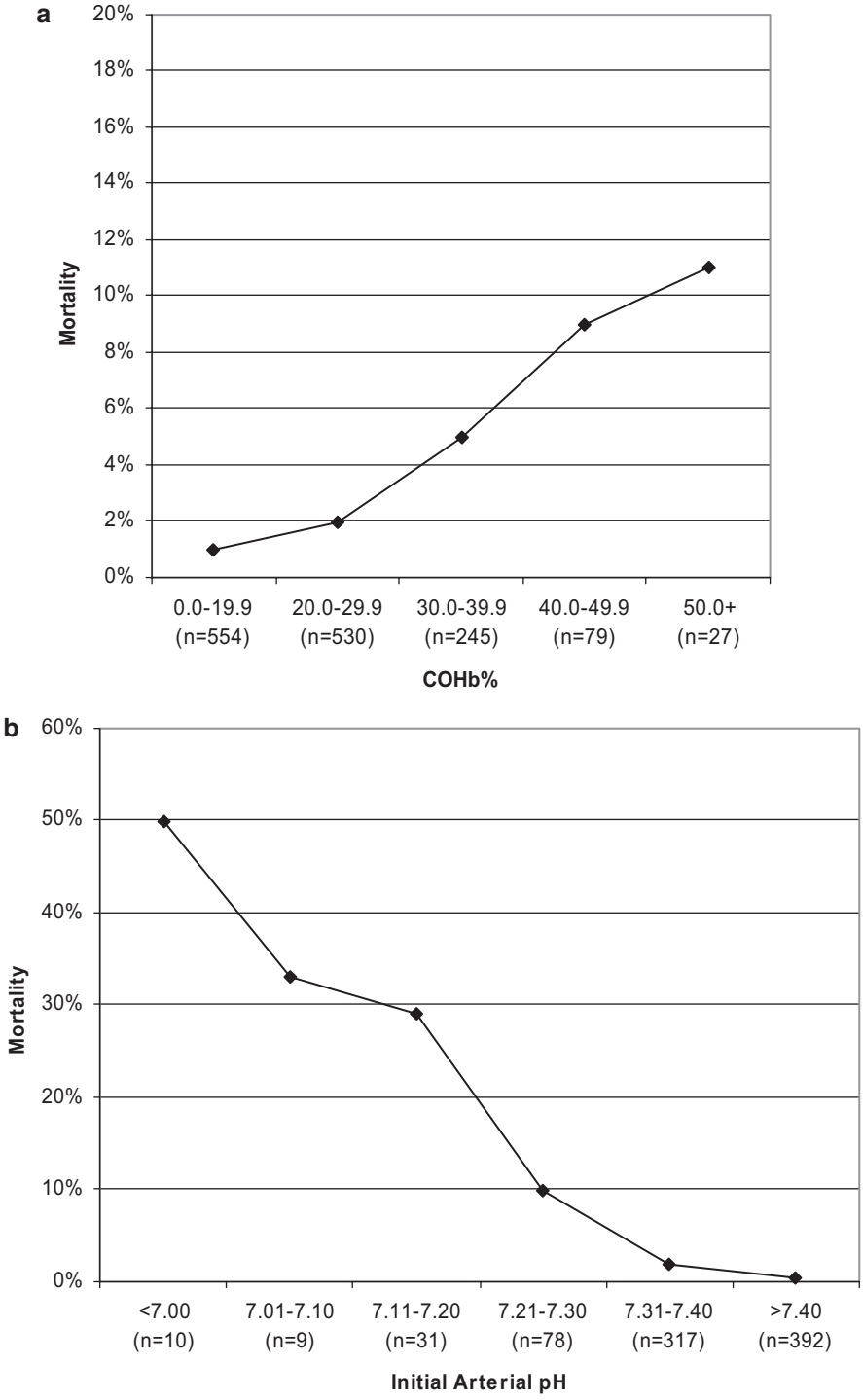

Figure 2. (*a*) Mortality in acute carbon monoxide poisoning as a function of initial carboxyhemoglobin (*COHb*) level. (*b*) Mortality in acute carbon monoxide poisoning as a function of initial arterial pH.

A recent study of patients with cyanide poisoning not associated with smoke inhalation found similar correlations between arterial pH and both blood lactate ($r = 0.87$) and cyanide levels ($r = 0.91$) (17). In the present study, lower pH with equivalent COHb levels among both survivors and nonsurvivors exposed to CO from fires suggests the possibility that some could have suffered from combined CO and cyanide poisoning.

The degree of elevation of the carboxyhemoglobin level is sometimes used to

Table 2. Prior publications reporting mortality rates among a minimum of 100 carbon monoxide-poisoned patients treated with hyperbaric oxygen

Author	Patients	Type of Treatment	Deaths
Goulon et al. (5)	302	Hyperbaric oxygen 273 Normobaric oxygen 29	42
Mathieu et al. (6)	230	Hyperbaric oxygen 203 Normobaric oxygen 27	4
Myers et al. (7)	213	Hyperbaric oxygen 131 Normobaric oxygen 82	2
Norkool and Kirkpatrick (8)	115	Hyperbaric oxygen 115	11
Sloan et al. (9)	297	Hyperbaric oxygen 297	17
Raphael et al. (10)	629	Hyperbaric oxygen 459 Normobaric oxygen 170	4
Annane et al. (11)	343	Hyperbaric oxygen 173 Normobaric oxygen 170	0
Satran et al. (12)	230	Hyperbaric oxygen 230	12
Historical totals	2359	Hyperbaric oxygen 1881 Normobaric oxygen 478	92 (3.9%)
Present study	1473	Hyperbaric oxygen 1473	38 (2.6%)

estimate the severity of CO poisoning (18). The absolute nature of such categorization has been challenged (19) and some experts feel that the correlation between clinical deficits and measured COHb level is actually quite weak (20). In the recent study by Weaver et al. (21), COHb did not correlate with 6-wk cognitive outcome. In the present study, elevation of the COHb level did correlate significantly with mortality in univariate analysis (Table 1, Fig. 2*a*) but extremely low arterial pH, when present, was more significantly associated with rate of death than extreme elevations of COHb level (Table 1, Fig. 2*b*).

It is possible that COHb level and loss of consciousness were not significantly associated with death in multivariate analysis because of factors particular to each of the two variables. Time from end of CO exposure to measurement of COHb was not recorded, thereby introducing the possibility that levels in some individuals would have been much higher if obtained immediately. Similarly, loss of consciousness was recorded only as having occurred or not. Duration of loss of consciousness or depth of coma for each patient is unknown. It is possible that persistent unconsciousness correlates better with mortality than transient unconsciousness. In fact, the presence of endotracheal intubation during hyperbaric treatment may correlate strongly with death because it is a marker for more severe loss of consciousness.

Because 20 decedents in the present study were exposed to CO from fires, the possibility that burns contributed their deaths must be considered. In one large study of 1,665 burn patients, BSA involvement greater than 40% was found to be a risk factor predictive of death (22). In the present study, 1 of 8 patients had this degree of burn injury (60%). "Burns" was coded as the cause of death for only this patient and one other who had 20% BSA involvement.

To summarize, the mortality rate of CO poisoning receiving hospital-based medical treatment, including hyperbaric oxygen, is approximately 3%. Characteristics significantly associated with mortality include fire as a source of CO, loss of consciousness, carboxyhemoglobin level, arterial pH, and presence of endotracheal intubation during hyperbaric treatment. Those designing future prospective studies should consider measurement of cyanide levels in patients exposed to CO from fires to determine its contribution to metabolic acidosis as a predictor of mortality.

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