Clinical aspects and management of poisonings with cyanide

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Introduction

- Cyanide: a potent intracellular poison, with attachment to the ferric form of necessary enzymes (cytochrome oxidase, succinic dehydrogenase, superoxide dismutase, ...)
- It results in tissue hypoxia, acidosis, and death.

- Recognition of a non-classical situation of CN poisoning may be difficult.
- Laboratory diagnosis may take hours to days
- Early aggressive treatment with appropriate antidotes is essential
The spectrum of cyanide poisoning

- HCN (50 ppm, 30 min; 200-400 ppm, 1-2 min)
- CN salts: CN Na
  CN K
  CN Hg, ...
  CN Au
  CN Br, CN Cl
- Nitriles: Acetonitrile: $\text{CH}_3\text{CN} \rightarrow \text{HCN} + \text{CH}_2\text{O}$
  Propionitrile, ...
- Nitroprusside
- Cyanogenic plants
- Stored CN salts: CN $\rightarrow$ CNO
Conditions resulting in exposure to cyanide or cyanogen compounds

- **Household exposure**: residential fires (pipe, furniture, organic, plastics)
- **Industrial incidents**: fumigation, photographic chemicals, metallurgy, electroplating, organic synthesis, fertilizers
- **Individual or mass suicide**
- **Therapeutic exposure** to drugs such as nitroprussiate and laetrile
- **Dietary exposure** to plants such as cassava
- **Terrorist attack** (non persistent lethal agent):
  - Contamination of water
  - Food containing cyanogen compounds
  - Dispersion of cyanide gas in a closed space
  - Vector facilitating skin penetration
Smoke inhalation (1)

Each year in France:
- 250,000 fires (58% residence fires)
- 4,000 victims (< 30% burnt)
- 400 deaths

In the US: Mortality rate: 0.98 deaths / 100,000 inhabitants
Smoke inhalation (2)

Fire may expose to 3 dangers:
- Thermal risk (flames, heated gases)
- Traumatic risk (blast, defenestration)
- Chemical risk

Smoke inhalation associates:
- Neurological and cardiac anoxic systemic injuries
- Ocular and respiratory irritant injuries

~ 80% of deaths are related to toxic smoke inhalation:
- Early death \((\text{per exposition})\) 80%
- Late death \((\text{post-exposition})\) 20%
Smoke composition

Polyintoxication: combustion or pyrolysis products in fire smokes

Compounds responsible of direct cellular anoxic toxicity:
• Carbon dioxide \((CO_2)\)
• Carbon monoxide \((CO)\)
• Hydrogen cyanide \((HCN)\)
• Anhydro- derivates: sulfur dioxide, hydrogen sulfide
• Nitric oxide \((NO)\)

Compounds responsible of mucous membrane irritant toxicity:
• Soot (particulates of polycyclic nitric and carbon compounds)
• Aldehydes: acrolein, formaldehyde, butyraldehyde, acetaldehyde, ...
• Nitrous derivates: nitric oxide and ammonia, isocyanides and amines
• Mineral acids: hydrochloric, hydrofluoric, hydrobromic acids, ...
• Carbon halogenated oxides: phosgene, chlorine
• Water vapors

Composition varies with environment

**CN:** residential fires, including pipe and furniture, organic materials, plastics (polyurethane), and melanin resines
Smoke inhalation ≠ CO poisoning

Post-mortem HbCO in 57 fire victims
Exposition duration: 30 min

Post-mortem HbCO in 54 cases of fatal CO poisoning
Exposition duration: 8 à 12 h

Teige et al. Z Rechtsmedizin 1977
Relationship between N content and CN production

Relationship in vivo between CN and HbCO

Ballentyne B. Clinical and experimental toxicology of cyanides, 1987

Bertol E. Forens Sci Int 1983
Pathways of cyanide toxicity

A potent intracellular poison, with attachment to the ferric form of necessary enzymes (cytochrome oxidase, succinic dehydrogenase, SOD). CN poisoning results in tissue hypoxia, acidosis and death.

CN levels in fire-related deaths

- Toxic cyanide levels (> 1 mg/l or > 39 μmol/l)
- Non-toxic cyanide levels

13% in Toxic cyanide levels and 87% in Non-toxic cyanide levels.
Pathways of cyanide toxicity and detoxification

\[ \text{OxyHb} \rightarrow \text{MetHb} \rightarrow \text{CyanoMetHb} \rightarrow \text{CN + MetHb} \rightarrow \text{CN} + \text{MetHb} \]

\[ \text{Rhodanese} + \text{S} \rightarrow \text{SCN} \rightarrow \text{OxyHb} \rightarrow \text{MetHb reductase} \rightarrow \text{O}_2 \rightarrow 2 \text{H}_2\text{O} \]
Increase of CN distribution into the brain with acidosis

Djerad A. Tox Sci 2001
Clinical presentation
Delay in onset of clinical manifestations

Seconds: HCN
Minutes: CN salts
Hours: Cyanogenic compounds:
- Nitriles
- Nitroprusside
## Clinical presentation

<table>
<thead>
<tr>
<th>Neurological</th>
<th>Respiratory</th>
<th>Cardiovascular</th>
<th>Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>Hyperpnea</td>
<td>HTA</td>
<td>Blood glucose</td>
</tr>
<tr>
<td>Restlessness</td>
<td>Central apnea</td>
<td>Shock</td>
<td>Lactate</td>
</tr>
<tr>
<td>Anxiety</td>
<td>+ Pulmonary edema</td>
<td>Cardiac arrest</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Confusion</td>
<td></td>
<td></td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Coma</td>
<td></td>
<td></td>
<td>Renal failure</td>
</tr>
<tr>
<td>+ Seizures</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Smoke inhalation

The two fundamental signs are:

1) **Soot in the airways** (nostrils, mouth, throats)
2) **Neurological impairment** (Headaches, dizziness, confusion, seizures, changes in mental status, coma)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbon monoxide intoxication</strong></td>
<td>83</td>
<td>63</td>
<td>43</td>
<td>92</td>
</tr>
<tr>
<td><strong>Cyanide intoxication</strong></td>
<td>98</td>
<td>56</td>
<td>28</td>
<td>99</td>
</tr>
</tbody>
</table>
## Vital signs in pure CO poisoning

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>CO (mmol/l)</th>
<th>SBP (mmHg)</th>
<th>HR (/min)</th>
<th>RR (/min)</th>
<th>Lactates (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe (n= 54)</td>
<td>2.87 ± 2.15</td>
<td>124 ± 19</td>
<td>88 ± 15</td>
<td>19 ± 4</td>
<td>3.2 ± 1.7</td>
</tr>
<tr>
<td>Moderate (n= 12)</td>
<td>0.84 ± 0.82</td>
<td>126 ± 18</td>
<td>85 ± 20</td>
<td>19 ± 3</td>
<td>2.3 ± 1.2</td>
</tr>
<tr>
<td>Mild (n= 65)</td>
<td>0.43 ± 0.56</td>
<td>125 ± 18</td>
<td>82 ± 13</td>
<td>19 ± 5</td>
<td>1.9 ± 0.9</td>
</tr>
<tr>
<td>Asymptomatic (n=15)</td>
<td>0.38 ± 0.45</td>
<td>128 ± 19</td>
<td>80 ± 6</td>
<td>17 ± 4</td>
<td>1.9 ± 0.7</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Benaissa ML. *Intensive Care Med* 2003
Diagnosis of cyanide poisoning

1- Cardiovascular impairment
   Hypotension, collapse, shock, or cardiac arrest
   Transient reversible cardiomyopathy

2- Abnormal respiratory pattern
   Polypnea, wide ventilation, hypopnea or apnea

3- Metabolic impairment
   Lactate concentration > 10 mmol/l in the presence of smoke inhalation without severe burns is strongly suggestive of CN (≥ 40 µmol/l) intoxication.

Se: 87 % - Spe: 94 % - PPV: 95 %

Baud FJ. NEJM 1991
### Occurrence of signs and symptoms in cases of CO and CN poisonings

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>CO (%)</th>
<th>CN (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>64</td>
<td>6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>43</td>
<td>33</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>31</td>
<td>NR</td>
</tr>
<tr>
<td>Coma</td>
<td>25</td>
<td>70</td>
</tr>
<tr>
<td>Dilated pupils</td>
<td>6</td>
<td>77</td>
</tr>
<tr>
<td>Seizures</td>
<td>3</td>
<td>34</td>
</tr>
<tr>
<td>Abnormal respiratory pattern</td>
<td>23</td>
<td>95</td>
</tr>
<tr>
<td>Pulmonary oedema</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Hypotension/shock</td>
<td>7</td>
<td>61</td>
</tr>
<tr>
<td>Plasma lactate (mM) + coma</td>
<td>2.8</td>
<td>13.4</td>
</tr>
</tbody>
</table>
### Clinical symptoms among 36 cyanide intoxications*

admitted to the Toxicological Intensive Care Unit at Fernand Widal Hospital in Paris, France

<table>
<thead>
<tr>
<th>Symptom</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>Cardiovascular collapse</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>Coma</td>
<td>13</td>
<td>36</td>
</tr>
<tr>
<td>Convulsions</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Respiratory arrest</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>18</td>
<td>50</td>
</tr>
<tr>
<td>Post-anoxic coma and death</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>6</td>
<td>17</td>
</tr>
</tbody>
</table>

* Intoxications by ingestion or inhalation, excluding smoke inhalation victims
# Type of Poison, Blood Cyanide and Plasma Lactate Concentrations, Clinical Status at the Time of Presentation, and Final Outcome in 11 Cases of Acute Cyanide Poisoning

<table>
<thead>
<tr>
<th>Type of Cyanide</th>
<th>Blood Cyanide (µmol/L)</th>
<th>Plasma Lactate (mmol/L)</th>
<th>Systolic Blood Pressure (mm Hg)</th>
<th>Respiratory Rate (b/min)</th>
<th>Glasgow Coma Score</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCN</td>
<td>256</td>
<td>53.0</td>
<td>40</td>
<td>0</td>
<td>3</td>
<td>Fatal</td>
</tr>
<tr>
<td>KCN</td>
<td>239</td>
<td>47.7</td>
<td>40</td>
<td>0</td>
<td>3</td>
<td>Fatal</td>
</tr>
<tr>
<td>Hg(CN)₂</td>
<td>217</td>
<td>19.6</td>
<td>60</td>
<td>ND</td>
<td>ND</td>
<td>Survival</td>
</tr>
<tr>
<td>CN salt</td>
<td>196</td>
<td>21.0</td>
<td>0</td>
<td>ND</td>
<td>ND</td>
<td>Fatal</td>
</tr>
<tr>
<td>KCN</td>
<td>158</td>
<td>8.6</td>
<td>160</td>
<td>25</td>
<td>15</td>
<td>Survival</td>
</tr>
<tr>
<td>KCN</td>
<td>154</td>
<td>13.6</td>
<td>110</td>
<td>8</td>
<td>12</td>
<td>Survival</td>
</tr>
<tr>
<td>KCN</td>
<td>150</td>
<td>17.7</td>
<td>95</td>
<td>0</td>
<td>3</td>
<td>Fatal</td>
</tr>
<tr>
<td>Au(CN)₂ - KCN</td>
<td>44</td>
<td>4.8</td>
<td>120</td>
<td>ND</td>
<td>ND</td>
<td>Survival</td>
</tr>
<tr>
<td>BrCN*</td>
<td>13</td>
<td>5.1</td>
<td>130</td>
<td>18</td>
<td>15</td>
<td>Survival</td>
</tr>
<tr>
<td>KCN</td>
<td>ND*</td>
<td>ND*</td>
<td>80</td>
<td>0</td>
<td>3</td>
<td>Survival</td>
</tr>
</tbody>
</table>

Baud F. *Crit Care Med* 2002
<table>
<thead>
<tr>
<th>Patients</th>
<th>Arterial pH</th>
<th>Arterial PaCO(_2) (mm Hg)</th>
<th>Arterial PaO(_2) (mm Hg)</th>
<th>Anion Gap (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.16</td>
<td>24.2</td>
<td>446.6</td>
<td>39.0</td>
</tr>
<tr>
<td>2</td>
<td>7.22</td>
<td>53.6</td>
<td>84.0</td>
<td>37.5</td>
</tr>
<tr>
<td>3</td>
<td>7.33</td>
<td>37.2</td>
<td>131.3</td>
<td>32.4</td>
</tr>
<tr>
<td>4</td>
<td>7.24</td>
<td>19.4</td>
<td>513.8</td>
<td>49.8</td>
</tr>
<tr>
<td>5</td>
<td>7.36</td>
<td>37.4</td>
<td>102.8</td>
<td>26.4</td>
</tr>
<tr>
<td>6</td>
<td>7.27</td>
<td>18.7</td>
<td>169.7</td>
<td>19.3</td>
</tr>
<tr>
<td>7</td>
<td>7.38</td>
<td>27.0</td>
<td>491.3</td>
<td>29.3</td>
</tr>
<tr>
<td>8</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>9</td>
<td>7.38</td>
<td>48.0</td>
<td>65.3</td>
<td>21.7</td>
</tr>
<tr>
<td>10</td>
<td>7.57</td>
<td>22.8</td>
<td>94.2</td>
<td>21.4</td>
</tr>
<tr>
<td>11</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: denotes not determined.
Correlation between the plasma lactate concentrations and the systolic blood pressure, the arterial pH, and the anion gap before antidotal treatment

Baud F. *Crit Care Med* 2002

\[ r = 0.87 \quad p = 0.002 \]

\[ r = 0.87 \quad p = 0.0004 \]

\[ r = 0.83 \quad p = 0.008 \]
Correlation of blood cyanide and plasma lactate before antidotal treatment

Before antidotal treatment:

- The median plasma lactate concentration was 18.6 mmol/L
- The median blood cyanide concentration was 155.9 μmol/L.

Baud F. *Crit Care Med* 2002
Relationship of plasma lactate concentrations to blood CN levels in a patient with pure acute CN poisoning

Baud F. *BMJ* 1996

CN: $256 \, \mu\text{mol/l}$ - T1/2: 1.14 h

Lactate: $53 \, \text{mmol/l}$ - T1/2: 3.94 h
Origin of lactate in poisonings?

- Lactic acidosis is not specific. Various toxicants can induce lactic acidosis: CO, Azide, H₂S, ...

- Several factors can contribute to lactic acidosis:
  - Cardiovascular failure
  - Apnea
  - Seizures
  - Acute liver failure
  - Catecholamine rush
  - Mitochondrial dysfunction
Interest of lactate measurement in cyanide poisoning

Sensitivity: 94%
Specificity: 70%
PPV: 64%
NPV: 98%

Baud F. *Crit Care Med* 2002
TK-TD relationships in 2 cases of CN poisoning

\[
E = E_{\text{max}} \times \frac{C^n}{[C_{50}^n + C^n]} + E_0
\]

Baud F. *Crit Care Med* 2002
**Does Cyanide toxidrome exist?**

Most frequent presentation = Rapid onset of (N = 86)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological symptoms</td>
<td>73 %</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>71 %</td>
</tr>
<tr>
<td>Seizures</td>
<td>30 %</td>
</tr>
<tr>
<td><strong>Cardiovascular symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>99 ± 33 / min</td>
</tr>
<tr>
<td>Reduction in SBP</td>
<td>103 ± 30 mmHg</td>
</tr>
<tr>
<td>Abnormal respiratory pattern</td>
<td>92 %</td>
</tr>
<tr>
<td>without pulmonary edema</td>
<td>94 %</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>7.20 ± 0.24</td>
</tr>
<tr>
<td>lactate increase</td>
<td>16.9 ± 11 mmol/l</td>
</tr>
<tr>
<td>SvO$_2$ arteriolization</td>
<td>89.5 ± 6.2%</td>
</tr>
<tr>
<td>Cardiac arrest (10 %), death (24 %)</td>
<td></td>
</tr>
</tbody>
</table>
Conventional treatment of CN poisoning

Conventional treatment of cyanide poisoning includes

- Decontamination
- Supportive treatment
- Specific treatment: antidotes
Decontamination

- Decontamination attempts to decrease the bioavailability of cyanide.
- Decontamination should be adapted to the conditions of cyanide poisoning.
- Does decontamination improves the prognostic of this poisoning?

Decontamination should be performed but never postpone supportive treatment.
Supportive treatment

- **Basic life-support of CN poisoning includes:**
  1. Immediate administration of high flow of oxygen,
  2. Protection of the airways,
  3. Cardiopulmonary resuscitation.

- **Advanced life support includes:**
  1. Endotracheal intubation in comatose patients
  2. Anti-epileptic drugs in case of seizures,
  3. Epinephrine infusion to correct cardiovascular collapse,
  4. Sodium bicarbonate to correct deep metabolic acidosis.

- Supportive treatment is efficient in pure CN poisoning.
THERAPEUTIC OPTIONS IN CYANIDE POISONING

Hyperglycemia

Lactic acidosis

Bradypnea

Coma

Seizures

Shock

As many supportive cares as organ failures
THERAPEUTIC OPTIONS IN CYANIDE POISONING

- Bradypnea
- Coma
- Hyperglycemia
- Lactic acidosis
- Seizures
- Shock

Oxygen + hydroxocobalamin + sodium thiosulfate
A combination treatment for all symptoms
Therapeutic strategies of this rare poisoning should take into account for the most common cause of cyanide poisoning in western countries, i.e. smoke inhalation which always results in a poly-intoxication involving CO.

An emergency antidote is an available drug allowing a right to error = safety first + proven efficiency
The list of antidotes to cyanide

- Oxygen
- Methaemoglobin forming agents
  - Nitrites
  - DMAP (dimethylaminophenol)
- Cobalt compounds
  - Dicobalt EDTA
  - Hydroxocobalamin
- Sulfur donors
  - Thiosulfate
The only available FDA-approved antidote in the US until 6 years ago was the **Pharmaceutical Cyanide Antidote Kit**

Contains 3 components:

- **Amyl nitrite pearls:**
  In the absence of IV access, gauze sponge - 1 gauze sponge, 30 sec each min or held between the $O_2$ source and the patient's mouth.

- **A solution of 3% sodium nitrite:**
  10 ml (0.33 ml/kg) IV 2-4 min, diluted in 100-150 ml solution
  Repeat at half the initial dose in the absence of response
  Produce 30% MetHb + Vasopressors (hypotension, vasodilatation)

- **25% sodium thiosulfate:**
  50 ml (1.65 ml/kg)

Fe$^{3+}$metHb + CN-Fe$^{3+}$Cytaa$_3$  \[\rightarrow\]  CN-metHb

*I do not use it*
Dicobalt EDTA (Kelocyanor®)

- Currently used in Europe but not available in the USA
- Dose: 300-600 mg IV over 2-5 minutes
- Repeat dose in case of no improvement
- Adverse effects: tachypnea, cardiovascular and hemodynamic instability, seizures, gastrointestinal symptoms, angioedema, allergic manifestations

Marrs TC. *Clin Tox* 2016

I do not use it
Thiosulfate

- Rhodanese, a sulfur transferase located in the mitochondria: irreversible transfer of a sulfane donor from thiosulfate to CN.
- Large doses required, since poor intracellular penetration. Limited interest in acute poisoning since slow detoxification ($t_{1/2}: 26 \text{ h}$).
- Dose: 8 - 16 g, continuous infusion, after initial bolus.
- Useful in nitrile poisoning (CN hepatic production).

\[
\text{CN-Fe}^3+\text{Cyt.Ox a3 + Na}_2\text{SO}_3 \rightarrow \text{Thiocyanates}
\]
Hydroxocobalamin (Cyanokit®)

- Currently used in Europe and recently in the USA
- 50 g of hydroxocobalamin to bind 1 g of CN
- Dose: 5 g (70 mg/kg in children, < 5g) IV (15 min), repeated according to seriousness (10g; 140 mg/kg).
- Ability to pass through the blood-brain barrier
- Adverse effects: reddish discoloration of the skin and urine, allergic reactions

Hydroxocobalamin molecule

\[
\text{CN-Fe}^3+\text{Cyt.Ox a3} + \quad \text{OH} \quad \text{CN} \\
\overset{\text{Hydroxocobalamine}}{\downarrow} \quad + \quad \overset{\text{Fe}^3+-\text{Cyt. Ox a3}}{\downarrow} \overset{\text{Cyanocobalamine}}{\downarrow}
\]
Intraosseous vs. intravenous infusion of hydroxocobalamin to treat acute severe cyanide toxicity in a swine model
Assessment of hydroxocobalamin efficiency in experimental studies of cyanide poisoning

Fifty-four beagle dogs were poisoned by IV administration of a potentially lethal dose of potassium cyanide.

Borron SW. *Clin Tox* 2006
Prospective study of fire victims treated with empiric hydroxocobalamin

67% survivors among the 42 patients confirmed *a posteriori* to have had CN poisoning.

Well-tolerated treatment irrespective of the presence of CN poisoning.

Utility and outcomes of hydroxocobalamin use in smoke inhalation patients

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 273)</th>
<th>Hydroxocobalamin (n = 138)</th>
<th>No hydroxocobalamin (n = 135)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 day creatinine difference</td>
<td>0.09 (−0.05 to 0.29)</td>
<td>0.09 (−0.04 to 0.24)</td>
<td>0.08 (−0.50 to 2.81)</td>
<td>0.95</td>
</tr>
<tr>
<td>(mg/dL), median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia, n (%)</td>
<td>97 (35.5)</td>
<td>31 (22.5)</td>
<td>66 (48.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ventilator days*, median (IQR)</td>
<td>5.0 (2–13)</td>
<td>4.0 (1–10)</td>
<td>7.0 (3–16)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vent-free days (VFD)*, median (IQR)</td>
<td>15.0 (0–25)</td>
<td>20.0 (0–26)</td>
<td>11.0 (0–24)</td>
<td>0.02</td>
</tr>
<tr>
<td>ICU LOS, days, median (IQR)</td>
<td>6.0 (2–15)</td>
<td>6.0 (2–13)</td>
<td>10 (4–20)</td>
<td>0.03</td>
</tr>
<tr>
<td>HLOS, days, median (IQR)</td>
<td>10.0 (3–20)</td>
<td>7.0 (3–18)</td>
<td>11.0 (5–24)</td>
<td>0.06</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>78 (28.6)</td>
<td>40 (29.0)</td>
<td>38 (28.1)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Routine administration was associated with lower rate of pneumonia, faster liberation from the ventilator, and reductions in ICU stay

Nguyen L. Burns 2017
Prehospital administration of hydroxocobalamin for smoke inhalation-associated CN Poisoning: 8 years of experience in the Paris Fire Brigade

Fortin JL. Clin Toxicol 2007
Cardiac disorders in smoke inhalation-associated CN poisoning

<table>
<thead>
<tr>
<th>Cardiac Disorder</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiocirculatory arrest</td>
<td>58</td>
</tr>
<tr>
<td>Asystole</td>
<td>5</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>41</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>56</td>
</tr>
<tr>
<td>Rhythm disorders</td>
<td>135</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>5</td>
</tr>
<tr>
<td>Subendocardial lesion</td>
<td>7</td>
</tr>
<tr>
<td>Conduction disorders</td>
<td>5</td>
</tr>
<tr>
<td>Intracardiac</td>
<td>1</td>
</tr>
</tbody>
</table>

61 patients with cardiorespiratory arrest

30 patients died at the scene despite antidotal treatment:
- 24 adults + 6 children
- Mean adult hydroxocobalamin dose used = 4.37 ± 1.10 grams
- Mean pediatric hydroxocobalamin dose used = 2.30 ± 0.44 grams

26 patients who recovered spontaneous cardiac activity after antidotal treatment with subsequent death in hospital:
- 24 adults + 2 children
- Mean adult hydroxocobalamin dose used = 6.04 ± 2.07 grams

5 adult patients surviving without any sequelae, particularly neurological:
- Mean adult hydroxocobalamin dose used = 7.50 ± 2.5 grams
- Mean cyanide levels before antidotal administration = 4.76 ± 1.92 mg/L [3.4–6.12 mg/L]

Fortin JL. J Emerg Med 2010
Hospital algorithm

ESEM 2012 guidelines
Typical PK profile from a severely CN poisoned patient treated with a 5-g hydroxocobalamin (OHCbl). The initial cyanide level was 128 µM. Formation of cyanocobalamin (CNCbl) was immediately observed, indicating the rapid complexation of cyanide by OHCbl, followed by the elimination of the excess OHCbl and the formed CNCbl.
- **Hydroxocobalamin** 5 g can bind all available CN for CN up to 40 μM.
- A cut-off of 300 μmol/L is the maximum amount of cyanocobalamin able to be formed after hydroxocobalamin 5 g dose.
- **Urinary cyanocobalamin** correlateq linearly with the initial blood CN for those patients with blood CN < 40 μM.

*Houeto P. Lancet 1995*
Interactions with other drugs

- HOCo mixed with $S_2O_3Na_2$
  
  unefficient thiosulphato-cobalamin

  *Evans CL. Br J Pharmacol 1964*

- HOCo is a chelating agent of NO

  *Rajanayagam et al. Br J Pharmacol. 1993*
Potential interference by hydroxocobalamin

Cooximetry hemoglobin measurement

Spectrophotometric assays on the Beckman Coulter DxC and AU680 analyzers: ALT, amylase, total bilirubin, cholesterol, creatine kinase, creatinine, magnesium, uric acid.
+ On the DxC: direct bilirubin, iron, phosphate, protein and triglycerides


Blood leak alarm interference by hydoxocobalamin is hemodialysis machine dependent

<table>
<thead>
<tr>
<th>Dialysis machine</th>
<th>Manufacturer</th>
<th>Is Pseudo-blood leak likely to happen with hydoxocobalamin use?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Althin</td>
<td>Baxter</td>
<td>No</td>
</tr>
<tr>
<td>C3</td>
<td>Cobe/Gambro</td>
<td>No</td>
</tr>
<tr>
<td>DBB 06</td>
<td>Nikkiso</td>
<td>Yes</td>
</tr>
<tr>
<td>DCS-6</td>
<td>Nipro</td>
<td>Unknown</td>
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<tr>
<td>Dialog Plus</td>
<td>B-Braun</td>
<td>Yes</td>
</tr>
<tr>
<td>Diapact</td>
<td>B-Braun</td>
<td>Yes</td>
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<tr>
<td>Diamax</td>
<td>Nipro</td>
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<tr>
<td>Formula 2000 Plus</td>
<td>Bellco</td>
<td>No</td>
</tr>
<tr>
<td>Formula 2000 Domus Plus</td>
<td>Bellco</td>
<td>No</td>
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<tr>
<td>Fresenius 2008K</td>
<td>Fresenius</td>
<td>Yes</td>
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<tr>
<td>MDS 101</td>
<td>Asahi</td>
<td>No</td>
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<tr>
<td>MR100B</td>
<td>C-THME</td>
<td>Unknown</td>
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<td>NCU-8</td>
<td>Nipro</td>
<td>Unknown</td>
</tr>
<tr>
<td>NxStage</td>
<td>NxStage</td>
<td>No</td>
</tr>
<tr>
<td>Phoenix</td>
<td>Gambro</td>
<td>No</td>
</tr>
<tr>
<td>Prismaflex</td>
<td>Gambro</td>
<td>No</td>
</tr>
</tbody>
</table>

Sutter ME. Clin Tox 2012
Avila J. Clin Nephrol 2012
The patients treated with hydroxocobalamin (n = 19) had an increased risk of AKI (OR: 5.8 [1.6–20.7]) and RRT (OR: 4.3 [1.09–17]). Association between AKI and hydroxocobalamin remained after adjusting for abbreviated burn severity index, SAPSII, and lactate on admission.
Regarding the main clinical condition of cyanide poisoning, i.e. smoke inhalation, we should take into account not only for the efficiency but also for the safety of the antidotal treatment.

- **Methemoglobin forming agents** impair the transport and delivery of oxygen to tissues.
- **Cobalt EDTA**: numerous side-effects.
- **Sodium thiosulfate** is safe.
- **Hydroxocobalamin** is safe. However, the risk of oxalate nephropathy cannot be excluded in the subset of critically burnt smoke-poisoned patients.
Nitroprusside and nitriles poisonings

- Adequate thiosulfate store = limiting step
- Treatment of life-threatening events: hydroxocobalamin
- Prevention of recurrent toxicity: sodium thiosulfate
- If persistent lactic acidosis: disulfiram to inhibit CN production

De Paepe P. Clin Tox 2016
Complications and sequellae

- Post-anoxic encephalopathy
- CO-related post-interval syndrome
- CN-related brain injuries

F 50 years, comatose, pulseless and apneic, CPR + 2.5 g Hcob + HBO
Blood cyanide (68 µM) HBCO (10.9%)

- Extrapyramidal hypertonia, choreo-athetotic movements
- MRI: increased cerebral atrophy, in the white matter, hemorrhagic putamini and globi pallidi; but respect of hippocampi

Baud FJ. BMJ Case Reports 2011
Experimental tested antidotes:

Nucleophiles (alphaketoglutarate, dihydroxyacetone):
- Bind to CN, reducing its availability to cytochrome oxidase
- Decreased toxicity in animal models
- Increased efficiency by the addition of thiosulfate

Other modalities under investigation:
- Isosorbide dinitrate
- Dinitrocobinamide (Vit B12 analogue, IM)
- Sulfanegen (3-mercaptopyruvate sulfurtransferase)
- NMDA inhibitors
- Nitrous oxide
- Antioxydants

Niknahad H. Toxicol Appl Pharmacol 1996
Take home message (1)

Both experimental and clinical data support the assumption that antidotal treatment is beneficial in cyanide poisoning.

- **Sodium thiosulfate:**
  - efficient - safe
  - delayed action

- **MetHb forming agents:**
  - potent
  - risk of impairment of oxygen delivery to the tissue

- **Cobalt EDTA:**
  - very potent - immediate action - effective if late
  - numerous side effects

- **Hydroxycobalamin:**
  - less potent - immediate action - safe
Take home message (2)

In patients suspected of CN poisoning:
- We recommend the use of hydroxocobalamin as first-line antidote according to its safety
- in association with supportive treatment
- administered as rapidly as possible.

In massive CN poisoning (ingestion) or nitriles poisoning, the potency of hydroxocobalamin even at high dose is limited.

The continuous infusion of sodium thiosulfate +/- disulfiram should be recommended.