



## Review

# Death will be the physician that cures: the treatment of rabies in the XIX century

*A morte será o médico que cura: o tratamento da raiva no século XIX*

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### Abstract

#### Introduction

Despite advances on antivirals and supportive therapy, treating rabies today is as challenging and hopeless today as it was in the XIX century. This disease causes 59,00 human deaths yearly and is 100% lethal, causing extensive suffering for the patients and their families.

#### Methodology

This article describes the approaches used by XIX physicians in order to treat the wounds of patients exposed to rabies and to treat patients already with rabies, based on a fictitious case inspired on accounts of the time.

#### Results and Conclusion

The efficacy of these approaches is discussed on the light of current knowledge on Biology and Pharmacology.

### Resumo

#### Introdução

Apesar dos avanços nos antivirais e na terapia de suporte, o tratamento da raiva hoje é tão desafiador e desesperador quanto era no século XIX. Esta doença causa 59 mil mortes humanas anualmente e é 100% letal, causando grande sofrimento aos pacientes e seus familiares.

#### Metodologia

Este artigo descreve as abordagens utilizadas pelos médicos do XIX para tratar feridas de pacientes expostos à raiva e para tratar pacientes já com raiva, a partir de um caso fictício inspirado em relatos da época.

#### Resultados e Conclusão

A eficácia destas abordagens é discutida à luz do conhecimento atual em Biologia e Farmacologia.

### Keywords

Rabies  
XIX century  
Treatment

### Palavras-chave

Raiva  
Século XIX  
Tratamento

Treating a patient with rabies today is neither more challenging nor more hopeless than it was before the availability of antivirals, Intensive Care Medicine and cutting-edge diagnostic tests. An estimated 59,000 human deaths occur annually, 95% of these in Africa and Asia, but cases also occur in the USA and Latin America; dog bites are the main source of rabies to humans worldwide, but bats, cats and wild carnivores are also relevant of a region-specific basis (1).

Wound care and vaccination followed by anti-rabies virus serum are 100% efficient in preventing the disease as a post-exposure prophylaxis, but failures on the recognition of exposure or in the supply and administration of immunobiologicals still account for a large number of patients who develop the disease and die, as rabies lethality is 100%.

To date, 11 out of 39 patients, including a Brazilian boy from Pernambuco State, survived after the so-called Milwaukee Protocol, first used in 2004 (2), which includes ribavirin, sapropterin, ketamin, benzodiazepines and phenobarbital in an Intensive Care Unit, while new approaches regarding antivirals and therapies are being developed.

From 2010 to 2025, 51 cases of human rabies occurred in Brazil while then main reservoir for humans changed from dogs to bats due to efficient dogs and cats vaccination and neutering programs, while marmosets (*Callithrix jacchus*) emerged as important transmitters in some of the northeastern States of Brazil (3).

Nonetheless, the medical and academic communities still regards rabies as incurable and most patients experience the full burden of the disease till their death with no palliation and devoid of proper medical care.

The aim of this article is to describe the medical approaches for post-exposure prophylaxis and attempted treatments in cases of rabies in humans during the XIX century by depicting the approaches for wound care and treatment of rabid patients in the form of a narrative review of a historical nature with critical and comparative analysis, using a fictional resource inspired by primary sources and 19th-century medical literature.

First, a plausible account by a physician at the dawn of the second half of the XIX, before Monsieur Pasteur's works, will be presented based on reports and style found in scientific publications of that period, collated from a series of historical sources and not from a single document. Though this is a fictional account, a context for the procedures described will be given afterwards.

"On August 2nd, 1864, at 4 past noon, Samuel B., a boy aged 9, son of a shoemaker in this city, was brought to this Hospital one day after being severely bitten by a dog that

attacked him unprovoked while the boy was making a delivery at Main Street as per his father's request. The dog was beaten to death by some coalminers that happened to be passing by and the stomach of the animal being removed, the gastric juice was poured over the wounds as a preventive to hydrophobia and its remains thrown to the river, the boy being taken home and the wounds dry with a piece of cloth and left undressed.

Upon inspection, the bite penetrated the left leg down to the gastrocnemius and the flexor carpi ulnaris on the left arm, the wounds occupying an area of teacup as the dog was said to be a bulldog, and the one on the arm seemed more severe as larger area of skin had been taken. Both wounds were still draining blood and showing a greenish edge suggestive of hematomas. The said boy was calm, had eaten his breakfast the normal way despite difficult to sleep due to the pain. Pulse strong and slow, 80 per minute. Tongue clear, no fever, no evacuations since previous morning. Conversation normal, talking about being an apprentice at his father's premises and not apparently shaken by the attack.

Hydrophobia being feared, I abundantly washed both wounds with cold water and then warm water and proceeded to excise the destroyed parts with a scalpel as recommended on these cases, this procedure being undertaken under chloroform. The use of gun powder was avoided as to prevent excessive bleeding, so I used the cautery instead. I next applied lapis infernalis and spirit of turpentine to the wounds, then dressed the wounds with a clean cloth to be changed and recommended lapis infernalis to be applied daily at home for the next seven days, after which the said boy was brought back to the hospital to be inspected, the wounds pouring the laudable pus, a known indication of a good prognostic. Being the boy in perfect health, he was dismissed.

October the 5th: Was brought back to this hospital by his mother. Had fever, headache, and a sore throat that started three days before. The wounds were healed and good scars were forming. Pulse Strong and fast, 110 per minute. I prescribed Peruvian bark to be administered as an infusion thrice a day for nine days to relieve the fever.

October the 12th: As per the father's request, I went to visit the boy at his house as his condition worsened. The boy was rather irritable and showing restlessness and reported a hard time getting to sleep. Pulse Strong and fast, 120 per minute. I gave the boy jalap, which induced a good purging with dark, foetid and consistent stool and recommended opium to be administered and a diet of wine, bread and pork.

October the 15th: Pulse weak and slow, 70 per minute. Could not ingest liquids and the simple view of a glass of water or the sound of flowing water caused terrible spasms on the throat, a definitive sign of the dread

hydrophobia. Much saliva was flowing from the mouth. I recommended calomel to increase salivation as an attempt to help to excrete the virus of hydrophobia via saliva and thus relieve the symptoms. Purging with ipecac was continued and I recommended sinapism to be applied to the epigastrium and spine and enema of laudanum. As the boy could not stand liquids, I recommended a diet of bread soak in milk, which he ingested easier.

October the 16th: The patient was very alert and talking about how he enjoyed fishing and that he was eager to learn how to write and read and that he wanted to be a physician, too. Asked for his preferred toy. Shades were closed to make his small room dark as light was bothering him. Pulse weak, slow, 70 per minute. Sinapism and jalap to be continued as well as laudanum enemata. Dose of calomel increased. Diet of bread soak in milk.

October the 17h: Condition much worsened. Could not recognise his family. Fell in a deep sleep and suddenly had a terrible convulsion. Pulse weak, slow, 60 per minute. Intense sweating. Pupils very dilated. When he wake up later that day, vomited a yellowish foamy liquid. Could not move arms, legs. Urine flowed involuntarily. I decided for bloodletting from the right arm, draining three cups of blood, much more than a normal bloodletting, as recommended in the cases of hydrophobia. Enema of laudanum and administered.

October the 18h: Was awoken for circa one hour by the morning. Asked for water, the fear of it already gone, with no spasms. Told he was afraid of a black dog that was hiding under his bed for many nights, but no real dog was there. Laudanum was given liberally. Slept or a few hours and woke up, then had a convulsion and passed away at 6pm.

Dissection of the body: The throat was reddish from the epiglottis down to the oesophagus. Lungs, bowels, kidneys & ct normal. Brain slightly congested."

First of all, during most of the XIX century, the word rabies was not applied to humans, but hydrophobia was used instead. But after the recognition that both diseases refer to the same pathological entity, rabies was proposed to be used in general, though the cause of the disease as a filterable agent, i.e., a virus, was determined only on 1903 (4,5). So, in the fictitious report above, the physician still refers to the disease as hydrophobia, which is a symptom of rabies restricted to humans and is inability to swallow liquids due to paroxysmal contractions of the pharynx as the patient attempts to drink (6).

At the beginning, it's stated that the dog attacked unprovoked. Rabies in dogs is mostly furious and, after 40 to 120 days of incubation, dogs might present aggressive, biting randomly as described.

In an attempt to prevent rabies, the wound of the boy was immediately treated with the gastric juice of the dog that attacked him; this was indeed a recommendation during the XVIII and XIX centuries and either the gastric juice of the aggressor animal or any other animal could be used (7). It is known that rabies virus can be inactivated by acids such as hydrochloric acid (8), so gastric juice of a carnivore could inactivate some of the virus in the wound. It is of note that then Italian physician Eusebio Giacinto Valli (1755-1816) prepared a rabies vaccine using saliva of rabid dogs and the gastric juice of frogs several years before Louis Pasteur's attenuated vaccine (9).

Washing the wound with cold and then warm water was also recommended to clean the wound in cases of bites, as well as excision of the bitten parts (including amputations) and the application of a cautery by a physician or a blacksmith in the form of a hot piece of iron were also recommended in the XIX century (10,11) and could speculatively decrease the virus load on the wound before it penetrates the neuromuscular junctions and starts the centripetal migration to the central nervous system via axons.

Gunpowder could be used instead of the cautery, but an author states it is not recommended as it could increase bleeding (7). Lapis infernalis ( $\text{AgNO}_3$ ), still used for cauterization, and spirit of turpentine, distilled from pine tree oil, were also recommended to treat bites to avoid rabies (7) and could have acted as virucides, though none of these mechanisms were known by then.

Despite the wound care, the fictitious boy on the report developed symptoms of rabies within a period of circa 2 months after being attacked by the dog, compatible with the reported incubation period for rabies of up to two months on average (12).

Nowadays, wound care regarding the attack of suspected animals is based on thoroughly washing the wound with a sponge and soap for at least 15 minutes, but without post-exposure prophylaxis (PEP) with infiltration of rabies immunoglobulin (RIG) in and around the wound, and vaccination, this simple wound care still might fail, as the one described in the report has. Nonetheless, by that time, physicians were much more aware of the risk of rabies than they currently are and several cases of human rabies still occur due to a lack of knowledge on rabies by physicians.

When the boy was brought back to the hospital eight days after the first visit, then physician states that "the wounds pouring the laudable pus, a known indication of a good prognostic". This is fully compatible with the medical mind of that age, as pus was mistakenly seen as a good evolution of the wound, in a time just before Joseph Lister's antiseptic concepts.

Upon his return to the hospital on October the 5th, the patient is on the prodromal phase of rabies that lasts up to 10 days and showing the unspecific symptoms of fever, headache, and a sore throat. The physician recommended Peruvian bark infusion, a very bitter-tasting anti-pyretic derived from *Cinchona* spp. trees containing quina, from which quinine was isolated in 1820, still used in its synthetic version chloroquine.

Sleep disturbances, anxiety, irritability and anorexia are symptoms that might appear during the progression of the prodromal phase and are compatible with those described in the report at October the 12th by the fictitious physician, who recommended opium, a largely used narcotic during the XIX century, besides jalap, made from the roots of *Ipomoea purga*, recommended as a cathartic used and loosely by that time (13). Wine, as he also prescribed, or strong beer, were recommended as stimulants in cases of rabies (14).

Despite the attempts to relieve the symptoms, the boy's condition worsened on the following day and hydrophobia manifested as the report tell us that he "Could not ingest liquids and the simple view of a glass of water or then sound of flowing water caused terrible spasms on the throat", so the diet is changed to bread softened in milk as it was known that solids were more easily ingested in cases of rabies than pure liquids.

By the time, it was thought that the excessive salivation was a way to clear the virus of rabies from the organism. The word virus here has nothing to do with Virology but is the Latin for the "poison" that caused rabies or other diseases as considered by that time. Besides, patients with rabies do not produce more saliva, but are unable to swallow the saliva, So, with the best of his knowledge, the physician recommended calomel ( $Hg_2Cl_2$ ), a panacea during the XIX century also recommended for rabies (15–20) that induces sialorrhoea due to mercury intoxication (21) in an attempt help the natural way to wash away the "poison" (22).

Enema of laudanum, as prescribed by the fictitious physician, was also recommended in cases of rabies as sedative (23). A tincture of opium, laudanum could be quickly absorbed by the intestinal epithelium and temporarily counteract the excitatory symptoms of rabies. Sinapism, i.e., the application of a mustard plaster to the skin as an irritant in an attempt to extract the disease by irritation, was also recommend when treating rabies (19).

The description of the patient's status by October 16th was based on the know evolution of the acute phase of rabies in humans, that might last up tom 14 days when the patient is not sedated and kept in an Intensive Care Unit, so the description of the fictious boy being alert and totally alert at times, keeping a normal conversation among periods of unconsciousness, besides

hydrophobia, photophobia, aerophobia and autonomic dysfunctions leading to bradycardia, hypertension and dyspnoea (24). At this moment, the physician decided to perform bloodletting, one of the tools of the so-called Heroic Medicine at that time, in an attempt to balance the humours. But, for rabies, a common bloodletting of a few ounces was not considered enough and a high volume of blood should be drained to cause fainting (25). Panic and hallucinations are also common in human rabies (24) and account for the fictious patient reporting he was afraid of a black dog that was hiding under his bed for many nights. It is of note that, at his last day of life, the boy asked for and could drink water: this is compatible to the knowledge that hydrophobia subsides at the latter phases of the disease.

At the autopsy, no major alterations were found but brain congestion, a description inspired on the lack of macroscopic findings in cases of rabies (26), also known by the time (11).

Though the procedures described in this fictious report to treat the wound can be efficient as virucides and avoid Rabies virus access to the neuromuscular junctions and thus rabies, the substances prescribed as treatments during the clinical phase of the disease have neither antiviral effects nor neuroprotective effects. The only thing that could have helped this "patient" was the administration of opium and laudanum as sedatives, Peruvian bark to relieve the fever, the use of milk and bread for hydration and nutrition and a room with low sensorial stimuli.

Interestingly, this is the exact approach currently recommended to manage human patients with rabies in the XXI century: a calm room without light, noise, wind etc, intravenous fluid hydration and electrolyte management, management of fever and sedation, without any antiviral (3). Followers of this paradigm compare the Milwaukee Protocol to the XIX Heroic Medicine and advocate those experimental therapies, including antivirals, should not be used at all, in accordance with Hippocrates' *Primum non nocere*.

Regarding wound treatment in the XIX century when rabies was feared, a host of further measures can be found in the literature of the time, essentially based on remedies that caused irritation to and cleaning of the wound, including caustics, warm oil, soap, sea bath, warm cow's milk (27–32) and even plantain (17). The effects of these remedies, if any, would be also of a virucidal character.

The treatments tried on patients already showing symptoms of rabies were even more varied. Chloroform was recommended both inhaled and per os (19,23) could have some effect on soothing the agitation and anxiety of the patient. Pills of *Cantharidae* powder per os,

obtained from blister beetles, were recommended (33) as *Cantharidae* powder was a known blistering agent used, as believed at the time, to irritate the skin and make a way for the cause of a disease to focus on the irritated part and be removed from the body. Though no effect on rabies could be expected on the light of our current pharmacological knowledge. Interestingly, Cantharidin, also a derivate form blister beetles, is still used topically today to treat viral diseases as molluscum contagiosum and warts.

Also, galvanism, *i.e.*, the application of electric currents to the body, be it of humans or other animals, either alive or dead, invented by the Italian physician Luigi Galvani (1737-1798) a novelty in vogue at the time, was recommended as a treatment for rabies (33,34).

Some rather obscure nostrums/ nostra, with no stable composition, were also used. On of these, named Ormskirk after a town in Lancashire, England, contained powdered chalk, alum, ammoniac, powder of elecampane (*Inula helenium*) root and oil of anise and was recommended *per os* in cases of rabies (31). Another example was James' powder (17), made of antimony trioxide (Sb<sub>2</sub>O<sub>3</sub>) and tricalcium phosphate (Ca<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub>). Flavonoids in *Inula* sp have been shown to have some antiviral properties (35,36), though not against rabies virus. But, besides their toxicity, nothing in the composition of these nostra have any effect on rabies. Arsenic, an omnipresent component of XIX pharmacopeia, but highly toxic, was also prescribed against rabies (29).

To relieve the difficulty in breathing and swallowing when hydrophobic installed, tracheostomy and also the application to the throat of a plaster made of camphor, musk, asafoetida (a resin from the roots of *Ferula* sp) and gum galbanum (from the same genus of plant) were recommended (28). Variations of the throat plaster could include opium and frankincense (29).

Other authors have recommended the use of sulphate of atropine injected hypodermically in heroic doses (37) and prussic acid (hydrogen cyanide, HCN) as a sedative (11). The anti-sialagogue/anti-vagal effect could help with the symptoms of rabies but was far from being a cure and hydrogen cyanide is indeed highly toxic.

Though taking place in the XVIII century, a quite radical treatment is of note: it was attempted in Florence when a man with rabies was treated by allowing a viper to bite both of his legs, but, unfortunately, he died 30 minutes after the treatment (38), either of rabies or the venom. This is of note as components of Iranian Caspian cobra (*Naja naja oxiana*) has been shown to have some *in vitro* antiviral activity against rabies virus (39), through none at that time had any clues on that.

The XIX physicians were quite aware of their limitations

as the dictum "Death will be the physician than cures" is cited in a case of rabies with a negative outcome (17) but, though did not know what they were doing, they did all they knew to save rabid patients. One key issue, though, was the specificity of their diagnosis, as many encephalitic diseases show similar symptoms to rabies and a positive outcome of their treatments could be biased by the presence of a less-lethal disease other than rabies.

Currently, mainly through drug repurposing, there is a plethora of antivirals against rabies virus testes *in vitro* and *in vivo* (40–42) and, as these drugs have already been approved for other uses in humans, their bench-to-bed pathway is shortened. We must get inspiration from the XIX century physicians and scientists and the knowledge provided by their colleagues in the XXI century.

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