



HAL
open science

Caring for patients with rabies in developing countries - the neglected importance of palliative care.

Arnaud Tarantola, Yoann Cabrol, Bangalore Jayakrishnappa Mahendra,
Sotheary In, Hubert Barennes, Hervé Bourhy, Yiksing Peng, Sowath Ly,
Philippe Buchy

► To cite this version:

Arnaud Tarantola, Yoann Cabrol, Bangalore Jayakrishnappa Mahendra, Sotheary In, Hubert Barennes, et al.. Caring for patients with rabies in developing countries - the neglected importance of palliative care.. Tropical Medicine and International Health, 2016, 21 (4), pp.564-7. 10.1111/tmi.12670 . pasteur-01429841

HAL Id: pasteur-01429841

<https://pasteur.hal.science/pasteur-01429841>

Submitted on 9 Jan 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

1 **Caring for rabies patients in developing countries - the**
2 **neglected importance of palliative care**

3 Arnaud Tarantola^{1,2}; Yoann Crabol¹ ; Bangalore Jayakrishnappa Mahendra³ ; Sotheary In^{1,2} ; Hubert
4 Barennes¹; Hervé Bourhy⁴; Yiksing Peng^{1,2}; Sowath Ly¹; Philippe Buchy⁵

5 1. Epidemiology and Public Health Unit, Institut Pasteur du Cambodge, Phnom Penh, Cambodia

6 2. Rabies Prevention Center, Institut Pasteur du Cambodge, Phnom Penh, Cambodia

7 3. Kodagu Institute of Medical Sciences, Madikeri, India

8 4. WHO Collaborating Centre for Reference and Research on Rabies, Institut Pasteur, Paris, France

9 5. Virology Unit, Institut Pasteur du Cambodge, Phnom Penh, Cambodia

10 6. GlaxoSmithKline, Vaccines Value & Health Sciences, 150 Beach Road, Singapore

11

12

13

14

15 Contact:

16 Arnaud Tarantola, MD, Msc

17 Head, Epidemiology and Public Health Unit

18 Institut Pasteur du Cambodge

19 5, Bvd. Monivong

20 BP 983 - Phnom Penh

21 Royaume du Cambodge

22 Mobile: +855 (0) 12 333 650

23 Fax: +855 (0) 23 725 606

24 Email: atarantola@pasteur-kh.org

25 **Ten years after “Management of rabies in humans” – a**
26 **developing country perspective**

27 **Key points**

28 Human rabies cases occur in rural developing settings where clinicians lack training and
29 medication. Even in resource-poor settings and using essential drugs, there is much
30 healthcare workers can do to help patients and families at no risk to themselves.

31 **Key words**

32 Rabies ; treatment ; palliative care; diazepam; midazolam; hydrophobia; developing countries

33 **Abstract**

34 Although limited publications address clinical management of symptomatic rabies patients in
35 intensive care units, the overwhelming majority of human rabies cases occur in the rural
36 setting of developing countries where healthcare workers are few, lack training and drugs.
37 Based on our experience, we suggest how clinicians in resource-limited settings can make
38 best use of essential drugs to provide assistance to rabies patients and their families, at no risk
39 to themselves. Comprehensive and compassionate patient management of furious rabies
40 should aim to alleviate thirst, anxiety and epileptic fits using infusions, diazepam or
41 midazolam and antipyretic drugs via intravenous or intrarectal routes. Although the patient is
42 dying, respiratory failure must be avoided especially if the family, after being informed, wish
43 to take the patient home alive for funereal rites to be observed. Healthcare staff should be
44 trained and clinical guidelines should be updated to include palliative care for rabies in
45 endemic countries.

46

47 In 2003, Jackson AC. et al. ¹ wrote a comprehensive and well-cited article on the
48 management of human rabies, duly reminding us of its dismal outcome, even in intensive
49 care units of resource-rich countries. As the authors then clearly stated, most human rabies
50 cases notified worldwide occur in developing countries where rabies remains a major and
51 probably underestimated public health issue ²⁻⁴, even emerging in some heretofore unaffected
52 territories. ^{5,6} Over a decade later, little has changed in terms of clinical management of
53 human rabies.

54 Not all persons who are bitten by a rabid animal become infected with rabies and human
55 patients have – in extremely rare instances - survived rabies, mostly in the New World. ^{1,7-15}
56 This is not the case with confirmed cases of human rabies acquired from dogs in the Old
57 World, which overwhelmingly have a lethal outcome: only two reported cases have survived
58 rabies in India, the country with the highest burden, but both had gross neurological
59 sequelae. ^{4,14,15}

60 Rabies cases occur mostly in rural settings of developing countries. ⁴ Few of the many dog
61 bite victims in countries such as Cambodia have access to timely and appropriate post-
62 exposure prophylaxis (PEP). ^{9,16} Worldwide, there are an estimated 59,000 human rabies cases
63 (and deaths) attributed to rabies each year. ⁴

64 To date, there is no effective and validated etiological treatment available for rabies once the
65 symptoms have set in and clinicians remain seemingly powerless. ^{8,17} This is particularly the
66 case in the rural developing setting where little or no intensive care is available or remains
67 beyond geographical or financial reach. What then can we do to aid rabies patients -
68 especially in rural areas - of developing countries?

69 Health care workers (HCW) in developing countries confronted with human cases of
70 suspected or confirmed rabies are not entirely helpless and their role remains essential. We
71 wish to remind readers of the specificities of managing rabies cases in the developing setting.
72 Diagnosis remains a priority when rabies PEP has been undertaken and failed.² Other people
73 potentially exposed to the same animal and those among the relatives and the healthcare
74 workers who would require PEP must quickly be identified. In approximately 20% of cases, a
75 "paralytic" presentation resembling Guillain-Barré syndrome will require little intervention
76 on the part of the clinical team. In most (80%) of cases, human rabies, febrile or otherwise,
77 will have a "furious" rabies presentation.^{18,19} Although the patient will most likely die,
78 prompt, effective and holistic compassionate clinical management can alleviate suffering for
79 the patients and their families. This can be performed even with extremely limited equipment
80 and drugs. If possible, the patient should be managed in a quiet and darkened room. Patient
81 privacy and dignity must be preserved. Management of furious cases with hydrophobia and
82 several days of fever, however, will require prompt and determined intervention, which must
83 first and foremost alleviate the sensation of thirst, which in our experience can be of mythical
84 proportions.²⁰ This can be done through infusion of 5% glucose solutions to compensate loss
85 of water²¹ or isotonic (0.9% NaCl) saline solution to compensate water and sodium loss,
86 being careful to immobilize the limb with a splint to prevent needle displacement.
87 Subcutaneous or intraperitoneal infusion are a useful alternative. Rather than restraint²²,
88 spastic signs and anxiety can be alleviated with diazepam which will also provide
89 myorelaxant²³, anticonvulsant²⁴ and sedative effects.²⁵ Diazepam is an affordable drug and
90 is widely available as a part of WHO's Model List of Essential Medicines²⁶. It can be
91 administered intravenously (IV) or intramuscularly or intrarectally (IR) (0.1-0.3 mg/kg IV
92 over 3-5 minutes in children or 0.5 mg/kg intrarectally ; 10 mg IV or IR in adults).²⁷ This can
93 be repeated every 1 - 4 hours and can be continued over 24 hours using IV infusion (3-10

94 mg/kg²⁷) if needed, guided by symptomatology, taking care to avoid respiratory depression.
95 The intrarectal route can be used at the same doses for maintenance therapy²⁸ if the infusion
96 cannot be maintained or if the patient is taken home by the informed family. Clinicians - and
97 families - should be aware of the risks of respiratory depression and aspiration. An effective
98 alternative, midazolam is included in WHO's List of Essential Medicine. Following a bolus
99 (depending on required level of sedation), midazolam can be administered at a dose of 1 mg
100 every 10 minutes by the intravenous route, taking care to reduce doses in
101 dehydrated/hypovolemic patients.^{26,29,30} Intramuscular or subcutaneous routes are also
102 possible. Lorazepam is another option, if available, which can also be administered
103 subcutaneously.³⁰
104 Treating fever by sponging may not be tolerated by a "furious" rabies patient, but alternating
105 or combined ibuprofen and paracetamol (also called acetaminophen) by non-oral routes
106 (intravenous, injectable or intrarectal) in patients with hydrophobia may provide some relief
107 by somewhat abating fever if it is present.³¹ Unfortunately, these drugs are often not available
108 in injectable form in the developing setting²⁶ and intrarectal paracetamol/acetaminophen
109 does not effectively provide analgesia in the short-term³²⁻³⁴.
110 Physical restraint is often used by health care teams who fear that rabid patients may harm
111 them or themselves. It may be useful to prevent infusion displacement or self-harm, but
112 should be used sparingly as it stimulates agitated patients. Restraints may be loosened as soon
113 as patients become sedated/more calm. After prompt albeit limited medical intervention has
114 offered whatever relief it can, local beliefs and economic constraints must be taken into
115 account, in agreement with the patient if possible and the family. In Cambodia, for instance,
116 the patient is usually sent home, preferably alive so that religious rites can be administered
117 and the family not be burdened with the added cost of returning home with a cadaver, which
118 is usually much more costly than with even a moribund patient. Planning for transport may

119 lead to preferring non-intravenous administration routes.
120 In developing countries - as probably elsewhere - HCW are fearful of contracting rabies
121 during care. Furthermore, whatever available health care is usually delivered in the first few
122 days or hours by family members potentially exposed to body fluids and without personal
123 protective equipment. Although the risk of transmission from human to human is considered
124 nil³⁵, their concerns must be addressed and they must be offered PEP (targeting Category
125 II)³⁶ following exposure to a human rabies case.^{1,10} This will help ensure they continue to
126 provide the best available care to suspected rabies patients.

127 The situation of many developing countries is well illustrated by that of Cambodia, a highly
128 enzootic country where only three PEP centers are freely accessible to the public.¹⁶ Much
129 work is needed on the part of the authorities to make PEP accessible after a potentially
130 infective dog bite in developing countries.⁹ A network of bite management centers must be
131 developed in rural areas while management of dog populations and systematic immunization
132 of dogs must be promoted countrywide.^{37,38} As clinical guidelines^{39,40} do not include rabies
133 management, much training and communication is also needed. The place of palliative care
134 in the management of rabies patients must be addressed in national and international
135 guidelines. This would help HCW in developing settings realize that - even if the rabies
136 patient will die - they can dramatically alleviate the suffering of rabies patients and their
137 families, at no risk to themselves.

138 **Acknowledgements**

139 We thank Drs. Cécile Aubron and Olivier Huet for their advice and editorial help.

140 **Declaration of competing interests**

141 No competing interests. Philippe Buchy is an employee of GSK Vaccines.

142

145 **References**

- 146 1. Jackson AC, Warrell MJ, Rupprecht CE, Ertl HCJ, Dietzschold B, O'Reilly M, Leach RP, Fu ZF,
147 Wunner WH, Bleck TP, Wilde H. Management of rabies in humans. *Clin Infect Dis Off Publ Infect*
148 *Dis Soc Am.* 2003;36(1):60-63. doi:10.1086/344905.
- 149 2. World Health Organization. *WHO Expert Consultation on Rabies (Second Report)*. Geneva,
150 Switzerland; 2013.
- 151 3. Coleman PG, Fèvre EM, Cleaveland S. Estimating the Public Health Impact of Rabies. *Emerg*
152 *Infect Dis.* 2004;10(1):140-142. doi:10.3201/eid1001.020744.
- 153 4. Hampson K, Coudeville L, Lembo T, Sambo M, Kieffer A, Attlan M, Barrat J, Blanton JD, Briggs
154 DJ, Cleaveland S, Costa P, Freuling CM, Hiby E, Knopf L, Leanes F, Meslin F-X, Metlin A, Miranda
155 ME, Müller T, Nel LH, Recuenco S, Rupprecht CE, Schumacher C, Taylor L, Vigilato MAN,
156 Zinsstag J, Dushoff J, on behalf of the Global Alliance for Rabies Control Partners for Rabies
157 Prevention. Estimating the Global Burden of Endemic Canine Rabies. Carvalho MS, ed. *PLoS*
158 *Negl Trop Dis.* 2015;9(4):e0003709. doi:10.1371/journal.pntd.0003709.
- 159 5. Putra AAG, Hampson K, Girardi J, Hiby E, Knobel D, Mardiana IW, Townsend S, Scott-Orr H.
160 Response to a rabies epidemic, Bali, Indonesia, 2008-2011. *Emerg Infect Dis.* 2013;19(4):648-
161 651. doi:10.3201/eid1904.120380.
- 162 6. Windyaningsih C, Wilde H, Meslin FX, Suroso T, Widarso HS. The rabies epidemic on Flores
163 Island, Indonesia (1998-2003). *J Med Assoc Thai Chotmaihet Thangphaet.* 2004;87(11):1389-
164 1393.
- 165 7. Jackson AC. Recovery from rabies. *N Engl J Med.* 2005;352(24):2549-2550.
166 doi:10.1056/NEJMe058092.
- 167 8. Hemachudha T, Ugolini G, Wacharapluesadee S, Sungkarat W, Shuangshoti S, Laothamatas J.
168 Human rabies: neuropathogenesis, diagnosis, and management. *Lancet Neurol.*
169 2013;12(5):498-513. doi:10.1016/S1474-4422(13)70038-3.
- 170 9. Tarantola A, Ly S, In S, Deubel V, Buchy P. Re: Only a sixth of animal bite victims in India get
171 antirabies treatment. October 2013. <http://www.bmj.com/content/347/bmj.f6040/rr/667136>.
172 Accessed January 8, 2014.
- 173 10. World Health Organization. WHO position paper on rabies. *Wkly Epidemiol Rec.*
174 2010;85(32):309-320.
- 175 11. Cleaveland S, Fèvre EM, Kaare M, Coleman PG. Estimating human rabies mortality in the
176 United Republic of Tanzania from dog bite injuries. *Bull World Health Organ.* 2002;80(4):304-
177 310.
- 178 12. Velasco-Villa A, Messenger SL, Orciari LA, Niezgodna M, Blanton JD, Fukagawa C, Rupprecht CE.
179 Identification of New Rabies Virus Variant in Mexican Immigrant. *Emerg Infect Dis.*
180 2008;14(12):1906-1908. doi:10.3201/eid1412.080671.

- 181 13. Willoughby RE Jr, Tieves KS, Hoffman GM, Ghanayem NS, Amlie-Lefond CM, Schwabe MJ,
182 Chusid MJ, Rupprecht CE. Survival after treatment of rabies with induction of coma. *N Engl J*
183 *Med.* 2005;352(24):2508-2514. doi:10.1056/NEJMoa050382.
- 184 14. de Souza A, Madhusudana SN. Survival from rabies encephalitis. *J Neurol Sci.* 2014;339(1-2):8-
185 14. doi:10.1016/j.jns.2014.02.013.
- 186 15. Madhusudana SN, Nagaraj D, Uday M, Ratnavalli E, Kumar MV. Partial recovery from rabies in a
187 six-year-old girl. *Int J Infect Dis IJID Off Publ Int Soc Infect Dis.* 2002;6(1):85-86.
- 188 16. Tarantola A, Ly S, In S, Ong S, Peng Y, Heng NY, Buchy P. Rabies vaccine and rabies
189 immunoglobulin in Cambodia: use and obstacles to use. *J Travel Med* 2015. 2015;22(5):348-
190 352. doi:10.1111/jtm.12228.
- 191 17. Dacheux L, Delmas O, Bourhy H. Human rabies encephalitis prevention and treatment:
192 progress since Pasteur's discovery. *Infect Disord Drug Targets.* 2011;11(3):251-299.
- 193 18. Susilawathi NM, Darwinata AE, Dwija IBNP, Budayanti NS, Wirasandhi GAK, Subrata K, Susilarini
194 NK, Sudewi RAA, Wignall FS, Mahardika GNK. Epidemiological and clinical features of human
195 rabies cases in Bali 2008-2010. *BMC Infect Dis.* 2012;12:81. doi:10.1186/1471-2334-12-81.
- 196 19. Dacheux L, Reynes J-M, Buchy P, Sivuth O, Diop BM, Rousset D, Rathat C, Jolly N, Dufourcq J-B,
197 Nareth C, Diop S, Iehlé C, Rajerison R, Sadorge C, Bourhy H. A reliable diagnosis of human
198 rabies based on analysis of skin biopsy specimens. *Clin Infect Dis Off Publ Infect Dis Soc Am.*
199 2008;47(11):1410-1417. doi:10.1086/592969.
- 200 20. Grimal P. Tantalus. In: *Dictionnaire de la Mythologie Grecque Et Romaine.* Paris: Presses
201 Universitaires de France; 1999:608.
- 202 21. Simpson JN, Teach SJ. Pediatric rapid fluid resuscitation. *Curr Opin Pediatr.* 2011;23(3):286-292.
203 doi:10.1097/MOP.0b013e3283460599.
- 204 22. Dorfman DH. The use of physical and chemical restraints in the pediatric emergency
205 department. *Pediatr Emerg Care.* 2000;16(5):355-360; quiz 362-363.
- 206 23. Okoromah CN, Lesi FEA. Diazepam for treating tetanus. *Cochrane Database Syst Rev.*
207 2004;(1):CD003954. doi:10.1002/14651858.CD003954.pub2.
- 208 24. Walker M. Status epilepticus: an evidence based guide. *BMJ.* 2005;331(7518):673-677.
- 209 25. Mandrioli R, Mercolini L, Raggi MA. Benzodiazepine metabolism: an analytical perspective. *Curr*
210 *Drug Metab.* 2008;9(8):827-844.
- 211 26. WHO | WHO Model Lists of Essential Medicines. WHO.
212 <http://www.who.int/medicines/publications/essentialmedicines/en/>. Accessed January 8,
213 2014.
- 214 27. Broek I, Albajar P, Médecins sans Frontières. *Clinical Guidelines: Diagnostic and Treatment*
215 *Manual; for Curative Programmes in Hospitals and Dispensaries; Guidance for Prescribing.*
216 Paris: Médecins sans frontières; 2013. <http://www.webcitation.org/6YSuKGS1>.
- 217 28. Team APW. The use of rectal diazepam for the treatment of prolonged convulsions in children -
218 Australian Prescriber. <http://www.webcitation.org/6YSuRDQL2>. Accessed January 2, 2015.

- 219 29. WHO | Midazolam (Inclusion) -- Adults and Children. WHO.
 220 http://www.who.int/selection_medicines/committees/expert/18/applications/Midazolam/en/
 221 . Accessed May 19, 2015.
- 222 30. *Essential Medicines in Palliative Care*. World Health Organization; 2013.
 223 http://webcache.googleusercontent.com/search?q=cache:eRTPrfSpHPIJ:www.who.int/selection_medicines/committees/expert/19/applications/PalliativeCare_8_A_R.pdf+&cd=4&hl=fr&ct=clnk.
 224
 225
- 226 31. Wong T, Stang AS, Ganshorn H, Hartling L, Maconochie IK, Thomsen AM, Johnson DW.
 227 Cochrane in context: Combined and alternating paracetamol and ibuprofen therapy for febrile
 228 children. *Evid-Based Child Health Cochrane Rev J*. 2014;9(3):730-732. doi:10.1002/ebch.1979.
- 229 32. P Gaudreault JG. Pharmacokinetics and clinical efficacy of intrarectal solution of
 230 acetaminophen. *Can J Anaesth J Can Anesth*. 1988;35(2):149-152. doi:10.1007/BF03010655.
- 231 33. Varela ML, Howland MA. Single high-dose rectal acetaminophen in children. *Ann*
 232 *Pharmacother*. 2004;38(11):1935-1941. doi:10.1345/aph.1D340.
- 233 34. Viitanen H, Tuominen N, Vääräniemi H, Nikanne E, Annala P. Analgesic efficacy of rectal
 234 acetaminophen and ibuprofen alone or in combination for paediatric day-case adenoidectomy.
 235 *Br J Anaesth*. 2003;91(3):363-367.
- 236 35. Fekadu M, Endeshaw T, Alemu W, Bogale Y, Teshager T, Olson JG. Possible human-to-human
 237 transmission of rabies in Ethiopia. *Ethiop Med J*. 1996;34(2):123-127.
- 238 36. Rabies vaccines: WHO position paper--recommendations. *Vaccine*. 2010;28(44):7140-7142.
 239 doi:10.1016/j.vaccine.2010.08.082.
- 240 37. Lembo T, Partners for Rabies Prevention. The blueprint for rabies prevention and control: a
 241 novel operational toolkit for rabies elimination. *PLoS Negl Trop Dis*. 2012;6(2):e1388.
 242 doi:10.1371/journal.pntd.0001388.
- 243 38. Lembo T. Chapter 19 - Blueprint for Rabies Prevention and Control. In: Jackson AC, ed. *Rabies*
 244 *(Third Edition)*. Boston: Academic Press; 2013:671-681.
- 245 39. *Clinical Practice Guidelines for Medicine*.; 2013. <http://www.webcitation.org/6LpeQwmol>.
 246 Accessed December 13, 2013.
- 247 40. *Clinical Practice Guidelines for Paediatric*.; 2013. <http://www.webcitation.org/6LpefKrOM>.
 248