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► 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-01429841v1>

Submitted on 9 Jan 2017

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

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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 issue²⁻⁴, 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.

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