EDITORIAL COMMENTARY

# Diagnosis and Treatment of Botulism: A Century Later, Clinical Suspicion Remains the Cornerstone

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**(See the article by Wheeler et al. on pages 1669–73)**

"I know pornography when I see it," wrote Supreme Court Justice Potter Stewart [1]. The immediate clinical diagnosis of botulism and the key therapeutic decision in its management—administration of botulinum antitoxin—depend on a similar logic. That is, one has to know, or at least suspect, botulism at first sight to treat it properly. Laboratory confirmation by the mouse bioassay, the standard diagnostic test for decades, can take ⩾1 day to provide a definitive answer, is costly, and requires an animal facility [2]. Detectable toxin in the serum may be present transiently or at low levels [3]. The first diagnostic assay for botulism, developed during an outbreak investigation in 1896, was to feed the suspected food to experimental animals [4]. The current mouse assay, based on intraperitoneal injection of the mouse with serum or with fluid extracts of feces, foods, or culture broths, was standardized in the 1970s [5].

In the accompanying article by Wheeler et al. [6] from the California Department of Public Health, the authors calculate the sensitivity of the mouse bioassay for clinically defined cases of wound botulism. Wheeler and colleagues surely know wound botulism when they see it, because they consult on most wound botulism cases, and to the mind of most experts familiar with the diagnostic challenges of botulism, they are fully justified in using clinical diagnosis as the gold standard against which to measure the mouse bioassay's limited sensitivity. The sensitivity calculated in the article is not the intrinsic sensitivity of a test under ideal laboratory conditions, but rather that of the clinical setting, calculation of which depends on a complicated set of real-world factors. This calculation must take into account the quality of the gold standard clinical diagnosis, which depends on the initial astuteness of the admitting physician and the diagnostic skill of the California Department of Public Health consultant, and variations in toxin levels in clinical samples, which depend on the timeliness of sample collection, the size of the *Clostridium botulinum* colony in the infected wound, kinetics of toxin absorption from the abscess, its migrations to the extracirculatory compartment, and possibly other factors.

One must also keep in mind that the sensitivity of mouse bioassay results may be different for the other principal forms of botulism—foodborne botulism and infant botulism. Most foodborne botulism cases are diagnosed by other expert consultants from Centers for Disease Control and Prevention (CDC) and the Alaska Department of Health and Social Services. Twenty-two public health laboratories perform the mouse bioassay for botulinum toxin and culture for *C. botulinum* in the United States. Detection of toxin in serum samples obtained from patients with foodborne botulism may depend on the timeliness of sample collection and probably on the ingested dose, the kinetics of intestinal absorption into the bloodstream, uptake by the extravascular compartment, and possibly other factors. Infant botulism is characterized by low circulating toxin levels, but high and persistent stool toxin levels; stool testing offers high diagnostic sensitivity. All of which is to say that the mouse bioassay sensitivity for clinical specimens from injection drug abusers in California reported in this article is probably a test characteristic specific to this condition in these individuals.

What, then, is the utility of the time-consuming, expensive laboratory tests, and why does the public health sector maintain extensive diagnostic capacity for such a rare disease? For the individual patient, confirmation of a serious diagnosis and definitive exclusion of other grave conditions, each with a different prognosis and requiring different therapy, is certainly desirable. In addition, only laboratory testing can provide information on toxin type.

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In the case of foodborne botulism, the ability to confirm the presence of toxin in a food can confirm epidemiologic implication of the food and the resultant emergency recall actions to protect the public. When unusual new botulism syndromes (e.g., adult colonization botulism), toxin types, and modes of transmission occur, their full description requires laboratory data.

What is the significance of the findings of Wheeler et al. [6] to the practicing physician who may encounter a case of possible botulism in the emergency department or in other clinical settings? This study reminds us that the key intervention for a patient with suspected botulism, administration of botulinum antitoxin, must be performed as quickly as possible according to the clinical findings. Awaiting laboratory confirmation is a grave error; moreover, in approximately one-third of cases, mouse bioassay results do not confirm an almost certain diagnosis. Failure to administer botulinum antitoxin may allow progression of paralysis, including that of respiratory muscles, resulting in respiratory collapse, death, or protracted hospitalization [7, 8]. Simply stated, a patient with *suspected* botulism should be treated as quickly as the antitoxin can be delivered to the bedside (like the mouse bioassay, botulinum antitoxin is an effective treatment from an earlier time—a despeciated equine serum product evocative of the preantibiotic, serum therapy era that reached its zenith in the 1930s [9]).

A clinician suspecting botulism in a patient should immediately call the state health department's 24-h emergency number. An expert clinical consultant will call the clinician back (California and Alaska have state-based clinical consultants; the CDC provides 24-hour emergency consultation for the other 48 states 7 days per week), and the state health department will initiate an epidemiologic investigation. If the illness is compatible with botulism, equine antitoxin treatment will be delivered immediately to the bedside from a supply that the CDC maintains in quarantine stations around the country. Clinical specimens and, in the case of suspected foodborne botulism, food samples will be tested at one of the public health laboratories capable of conducting the mouse bioassay for botulinum toxin and culturing *C. botulinum,* all at no cost to the patient [2, 7, 8]. The CDC botulism reference laboratory consults with laboratory colleagues and performs the diagnostic tests for those states that do not perform the tests themselves.

Developing and validating a diagnostic test more rapid, sensitive, and convenient than and as specific as the mouse assay would be an important step forward. However, the short-term clinical management of botulism will still depend on knowing botulism when we see it and then using the laboratory test for toxin to confirm the diagnosis in a portion of the cases.

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