REVIEW ARTICLE

The Controversial and Short-Lived Early Use of Rehydration Therapy for Cholera

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Oral rehydration treatment has prevented the deaths of millions of infants in the developing world. During the cholera outbreak of 1832 in Britain, 3 important advances in fluid therapy transiently emerged: intravenous fluid therapy, oral salt and water treatment, and chemical analysis of body fluids. William Stevens provided uncontrolled evidence that fluids and salt could prevent death, and William O'Shaughnessy found that water, salt, and carbonate were lost from the body in individuals affected by cholera and could be seen to be reduced in serum. Thomas Latta introduced intravenous fluid therapy. Early attempts to introduce oral fluid therapy failed to become established as cornerstones of clinical medicine because of a lack of convincing science and because of personal animosities. From the period just after World War II through the 1970s, the modern era of rehydration of patients with cholera and dehydrating diarrhea slowly developed, a process that may represent the finest example of translational research applying biochemical and physiologic observations to the clinic.

INTRODUCTION

The long history of rehydration in treating diarrheal diseases is associated with surprises and controversy. It was not until the mid-to-late 20th century that it was shown that intravenous fluid and electrolyte administration reversed ordinarily fatal cholera [1], and subsequently, the value of orally administered sodium, potassium, and glucose in the treatment of dehydrating diarrhea was shown [2]. In the 1970s, with the sponsorship of the World Health Organization, oral rehydration treatment was developed for widespread implementation in the developing world [3]. There was a rapid reduction in the number of infantile deaths from diarrhea-associated dehydration [4, 5]. Although a few early investigators had suggested that fluids could be beneficial in the management of cholera, most investigators at that time were critical of this approach.

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METHODS

Finding early references requires a starting point. In this case, it was Daniel Drake's review of William Stevens' 1832 article [6]. *The Lancet* and the *American Journal of Medical Sciences* were searched volume by volume for the period 1830–1850. The National Library of Medicine provided the early books; Stevens' 1853 book was located at the University of Chicago [7]. The Copenhagen University Library provided biographical information on William Stevens; a report on Stevens' honorary degree was obtained from the Oxford University Archives.

A BRIEF VIEW OF THE CURRENT STATUS.

Phillips first established that intravenous solutions could restore circulating blood volume and electrolyte deficits in patients with dehydrating cholera [1]. Further, cholera toxin was shown to stimulate the small bowel to secrete large quantities of sodium and potassium [8]. Fisher and Parsons discovered the mechanism of glucose transport in the gut [9]. Active absorption of glucose and absorption of sodium are interdependent; sodium absorption is enhanced by glucose [10, 11]. The bowel stimulated by cholera toxin can absorb large volumes of water even in the face of intense fluid

losses [3]. Careful clinical trials proved that oral rehydration was effective in reducing infant mortality from dehydration [4, 5]. Oral rehydration treatment was based on good laboratory-based science and may be the finest example we have of the use of translational research to improve medical care and reduce the rates of death.

THE EARLY HISTORY

The first description of cholera by a European came from Portuguese India in 1563 and was by Garcia da Orta [12]. The disease was well known in India throughout the 17th and 18th centuries. As the British East India Company and the British army asserted themselves on the subcontinent, classic cholera was appreciated; its clinical aspects were described.

From 1817 through 1820, several remarkable reports about cholera appeared in British publications. Those of James Jameson, William Scott, and Robert Steuart were most notable [13–15]. Later in the 19th century, Charles MacNamara provided a useful historical description of Asiatic cholera [16], also describing a temple to the cholera goddess, Oola Beebee, in Calcutta.

It seems quite possible that British commerce and military activities in India facilitated the spread of cholera within India and contributed to the westward pandemic movement in the 1830s from India across the international boundaries of Asiatic Russia, to western Russia, and into Western Europe [16]. At that time, there were no objective means to diagnose cholera. A clinical diagnosis was easy for full-blown cholera, but milder forms of illness were not considered to be cholera; therefore, incidence tabulations or various quarantine restrictions applied only to the worst cases, whereas mildly ill patients, who were uncounted and unrecognized, facilitated spread of the disease.

Without clear diagnostic boundaries, convictions concerning treatment and the success of treatment varied widely. The range of treatments that were advocated indicates the confusion and ineffectiveness of cholera treatment in general at that time.

In Britain and, subsequently, in the United States, treatment was firmly based on recognized principles. It was agreed that something in the bowel was causing the disease. How the poison was acquired remained a mystery, but it was not thought to be infectious. Treatment was based on removing the poison by purges, even though the spontaneous flow from the bowel was already great. No other consistent approach was advocated. At the core, management consisted of purging to remove the offending agents; opium was used to relieve associated cramps and possibly to slow the flow of fluid from the bowel. Beyond that, there was no other consistent therapy for severe diarrhea. Camphor, oral chloroform, lead acetate, and alcohol were each included in various treatment protocols from time to time in the early era of cholera treatment. Phlebotomy was common and was advocated even in the stage of circulatory failure secondary to fluid losses [17]. Throughout this time, treatment was acknowledged to be substantially ineffective.

Although it was generally agreed that cholera had not appeared in Britain or in Western Europe before 1831, Sydenham described a 1669 epidemic of what became known as English cholera. He advised that proper treatment should avoid popularly used cathartics but should include large volumes of broth derived from whole boiled chickens [18]. His therapy was an isolated break with tradition.

In 1831, as cholera became established in Russia, David Barry and William Russell were sent from London to St. Petersburg to investigate the disease. They gained firsthand experience with the clinical aspects of the disease. Both Barry and Russell were thoroughly convinced of the noncontagiousness of cholera and the efficacy of contemporary principles of treatment. Barry was a well-recognized British physician. As an Army surgeon, he had been severely wounded in the Peninsular War. Afterward, he had earned the MD degree in Paris. He was awarded a Fellowship in the Royal College of Physicians (London), the Emperor of Russia awarded him the Collar of St. Anne, and the King of Portugal gave him the Order of the Tower and the Sword of Portugal. Subsequently, in 1832, he was awarded a knighthood in England. Russell was knighted a few years later [19]. Barry was sent to Sunderland in northern England in 1831 when a violent disease appeared there. He recognized it as cholera. Sunderland was the first site affected by cholera in Britain [20, 21].

Meanwhile, William Stevens had developed a totally separate school of thought concerning the effects of "malignant tropical fevers" and severe diarrhea. At the time, Stevens lived in the Virgin Islands. The Islands had been under Danish rule, then under British rule during and after the Napoleonic War; they were subsequently ceded back to Denmark. A Scottish medical school had awarded Stevens an MD degree. He had trained as a surgeon and had been so successful that he was later offered a post on the faculty of surgery at his medical school. He had established a successful practice in the Virgin Islands while they were under British rule. When the transition to Danish control took place, he and other British physicians were examined in Copenhagen to determine their suitability for Danish practice. He was accepted as a member of the Danish Royal Academy of Physicians [22]. In the Virgin Islands, he had become impressed with the severity of tropical fevers. He observed that patients with yellow fever and other malignant tropical fevers developed a blackness of skin color and a darkening of their blood. He also became convinced that the normal scarlet color of arterial blood was produced by the loss of carbonic acid in the lungs in the presence of salt in the blood. Stevens observed that salt added directly to venous blood turned it red. Therefore, he tried an oral saline treatment for severely affected patients. The death rate decreased. He felt that salt was beneficial because

it restored blood to its normal color; in its normal state, blood was able to function normally. He seems to have had no understanding of the effect of the salt and fluid on blood volume [23].

As cholera swept the world in the early 1830s, it was observed that patients with severe cholera also developed blueness or blackness of the skin and that their arterial blood was blackened. It was not a leap for Stevens to deduce that giving extra salt to patients with cholera should also lead to improvement, and indeed, he observed significantly decreased mortality when he tried this technique. At that time, proving efficacy did not require study of a treatment cohort and comparison with an untreated control group. The empirical science on which he based his saline treatment is still difficult to understand.

Stevens had become a wealthy planter and successful island physician. He traveled widely to Western Europe and the United States advocating his salt therapy. In fact, he described successfully treating Genesee Valley Fever in Upstate New York [23]. He was in England during the 1832 cholera outbreak. Convinced as he was of the success of his mode of therapy, he persuaded the surgeon in charge of medical care at the Cold-Bath Fields Prison in London to try his fluid-salt treatment. Stevens reported that >200 patients were carefully treated there with his prescribed mixture of oral fluids containing sodium muriate, potassium chloride, and carbonate of soda. This fluid was administered in large volumes orally if the patient was not vomiting and rectally if vomiting hindered oral treatment. Stevens reported that only 1 in 30 patients with cholera died when treated with his salt solution. In a short time, those results and observations from others were reported in a short book Stevens published in Copenhagen [24].

Stevens bolstered his argument with measurements made by William O'Shaughnessy involving patients with cholera at Sunderland. O'Shaughnessy had found that the "peculiar dejected material" and blood showed large amounts of water, salt, and carbonate that had been lost from the body [25]. Thus, Stevens had another reason for administering large volumes of neutral salts and carbonate. He wanted to replace what had been lost. Yet others did not accept this radical change in thinking.

Perhaps most troublesome to this new management were the criticisms of Sir David Barry, by now the acknowledged British expert on cholera. He visited the Cold-Bath Fields Prison to observe Stevens' patients [26]. On two occasions, he concluded that the patients simply did not have cholera. This was confirmed by William O'Shaughnessy, who accompanied Barry on one of these occasions [27]. This difference of opinion was undoubtedly based on differences in diagnostic boundaries and a lack of the means of objective diagnosis. Although Barry did not engage in polemics, his word carried considerable weight.

Much of an ensuing bitter debate appeared in *The Lancet* and the *Medico-Chirurgical Review.* On 5 December 1831, James Johnson quoted from a letter from a Dr. Hackett in Trinidad, who charged that Stevens had misrepresented the beneficial effects of saline treatment in tropical fevers [28]. On 14 December 1831 and 9 January 1832, Stevens defended his position. In the 14 December note, he concluded that gossip had been circulated; he was glad to have it now in print. He said that "unfounded attacks, like venomous reptiles, are only dangerous when they crawl in the dark" [29, p. 412]. On 20 February 1832, during the next several issues of *The Lancet,* Stevens and Johnson exchanged further unpleasantries.

Published reviews of Stevens' papers and books on the effects of saline in the blood and for the treatment of cholera that were published in *The Lancet* were most unfavorable. The editor referred on one occasion to Stevens' "latest blunder." In another review of Stevens' cholera book, the editor indicated that it was more ingenious than it was sound [30]. James Johnson published a lengthy review of Stevens' text. He called it "the most trumpery book for its size that it has fallen our lot to review" [31, p. 321]. Johnson included correspondence from Barry and O'Shaughnessy refuting the Cold-Bath Fields Prison observations [31].

Finally, the editor of *The Lancet* concluded: "We have now done with the doctor [Stevens] and his doings, with the sights he has seen and the dreams he has expounded, we trust he will spare us and our readers the necessity of bestowing on him another niche in our immortalizing columns" [32, p. 90]. In 1832, the *American Journal of Medicine* presented the entire Stevens' argument and concluded that Stevens' position could not be accepted at that time. In 1832, the prominent American physician, Daniel Drake, discussed the saline treatment of Stevens and concluded that it was interesting but had not been sufficiently used to be endorsed [6].

Stevens was awarded an honorary Doctor of Civil Laws degree from Oxford University in 1834. Oxford records no longer indicate the reasons for the award. Stevens was swept along with 34 others at the Encaenia of 1834. This is said to have been an unusually large number, because it was the first assembly with the Duke of Wellington as Chancellor [33]. This award, however, did not change the attitude of medical authority toward Stevens and his work. In fact, the editor of *The Lancet* later referred to "the uncivil behavior of this new Doctor of Civil Laws" [34, p. 58].

In 1853, Stevens published his final book on the general subject of the treatment of cholera [7]. In this book, he recited details of the Cold-Bath Fields Prison experience, providing names and other details for all treated patients. The language was generally combative, and he blamed the nonacceptance of saline treatment on the pecuniary interests and pride of professional leaders. He recounted yet another attempt to seek endorsement from the Royal College of Physicians, but the President and other leaders, Stevens wrote, refused to modify

the earlier position. Further, Stevens accused Barry (dead by that time) of deliberately suppressing information about the success of saline treatment in Poland, Russia, and Sweden (where he felt that it had been particularly effective in Christiana). Stevens summarized by saying that the visits of Barry and O'Shaughnessy to the Cold-Bath Fields Prison had been superficial and brief. Further, they had merely reiterated biases that they had had before the visit [7]. The Stevens' 1853 text was also reviewed in *The Lancet*. The editor reported that he could not understand much of the author's physiology and pathology. Furthermore, the editor said he would not comment further on the extravagant polemics [34].

In 1989, J. E. Cosnett reviewed the origins of intravenous fluid therapy [35]. He credited O'Shaughnessy with an analysis of blood and stool in cholera, which had stimulated Thomas Latta to try intravenous injection of fluid with saline in 1832. Latta was, indeed, stimulated by O'Shaughnessy's report of concentration of the blood and loss of saline. He injected "copious volumes" using a silver tube and a syringe. He found that muriate of soda and subcarbonate of soda produced a good but not a lasting effect. Patients who had had rapid, feeble pulse and clouded consciousness were restored for 1–2 h. Some of these patients survived, but most experienced relapses of cholera and died of the disease [36].

Later in his life, O'Shaughnessy turned to other interests. He became fascinated by electricity and the development of telegraphy. O'Shaughnessy was knighted in 1856 for establishing the telegraph system in India. He also introduced the medicinal use of cocaine into Britain. His efforts in studying electrolyte deficits in patients with cholera were forgotten for almost 100 years [35].

Review of mid-19th century textbooks of medicine provides additional evidence of the general nonacceptance of saline therapy. In 1831, John Eberle described cholera but did not discuss treatment [37]. Sir James Watson, in 1844, provided perhaps the most damning assessment of saline treatment. He noted that "the proper plan is to arrest the diarrhea with opiates, astringents, or aromatics. Some say diluting the blood with neutral salts to liquefy or redden the blood and restore its circulation is proper. However it might be with pigs and herrings, salting the patient was not always the same as curing him" [17, p. 721]. Watson's book was adapted from his university lectures. He was probably the leading English physician of the time.

In 1848, Robley Dunglison recommended opiates, calomel, and cupping to the abdomen. He noted that carbonate of soda administered orally or in an enema had been recommended, but he said further, "the suspension of the absorption from the stomach makes little of this absorbed. Further, though this can dilute the serum, it does not remove the important mischief" [38, p. 145].

In 1866, Austin Flint did not recommend saline treatment for cholera [39]. By 1874, Frederick Roberts noted that "saline has proved ineffective" [40, p. 709].

CONCLUSION

William Stevens had in his hands the proper treatment of cholera and secretory diarrheas >100 years before oral rehydration therapy was finally established. Despite his discovery, he died in obscurity in England in 1868. Those responsible for the careful studies that proved the efficacy of oral rehydration therapy did not refer to the 1832 controversy.

Possible reasons for Stevens' failure:

1. His credentials were suspicious. He had been granted a degree by a Scottish medical school and was trained as a surgeon. He had established himself in the Caribbean islands, rather than earning credibility in Britain. He even dedicated his book to the King of Denmark!
2. His was a contentious personality. When confronted with disagreement, he returned abuse, thus initiating a cycle of ever-increasing hostility.
3. The science on which he based his treatment seemed improbable, even in 1832; Stevens attributed a strange prominence to a sodium effect on the color of blood; the significance of the phenomenon he described confused even his contemporaries.
4. There was no objective means of diagnosis of cholera. Severe cases were readily diagnosed; mild cases and the boundary between severe and mild cases was not recognized. Consequently, it was possible to dispute his diagnosis and, thus, the therapeutic effects of his treatment.
5. His ideas directly challenged recognized medical authorities.

The modern era of oral fluid-salt therapy moved quickly once the principles of intravenous treatment of cholera were at hand and the physiology of glucose-coupled sodium absorption had been documented.

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