

## An Outbreak of High Fever and Chills, Increased Blood Pressure, and Pruritus Among a Hemodialysis Unit

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Complications during hemodialysis are frequent and sometimes potentially fatal and peculiar in terms of etiology. We encountered an epidemic among our patients on maintenance hemodialysis in Fatemeh Zahra Hospital in Sari, Iran. In the summer of 2000, after the seasonal floods in the region, 2 patients on maintenance hemodialysis at Fatemeh Zahra Hospital were inflicted with fever of 39°C, chills, increased blood pressure, and generalized pruritus within 30 minutes after the beginning of hemodialysis session. All signs and symptoms ceased immediately after discontinuation of hemodialysis. We presumed these reactions to hypersensitivity to ethylene oxide; filters were thoroughly flashed with 2 liters of hypertonic saline solution and re-used. Ultimately, we replaced the filters by gamma-irradiated ones, but the episodes repeated. All angiotensin-converting enzyme inhibitors were discontinued, considering the probable role of these antihypertensive drugs in allergic reactions. Gradually, the epidemic spread among all the 50 patients with the same characteristics. In addition to the measures done for the first 2 patients, cultures were obtained from the municipal water before and after the reverse osmosis system and also the dialysate. The presence of exotoxin in the municipal and pre-reverse-osmosis water was checked several times, considering the possible water contaminating as a result of the recent floods, but no positive results was yielded.

To rule out any possible cause, hemodialysis process was done under a close supervision in all stages on volunteered patients with gamma-irradiated filters and thoroughly flashed lines with hypertonic saline solution, with no heparin, after discontinuation of all drugs. The same signs and symptoms occurred in the patients briefly after hemodialysis, which disappeared with its discontinuation. The patients were sent to other hemodialysis centers in the nearby cities, and a

special investigating group was sent by the Iranian Center of Dialysis. They decided to “autopsy” the hemodialysis machines. Precipitated formaldehyde was found in all the pipelines and connectors of the hemodialysis machines.

We performed first a sham-operated hemodialysis with hypochlorite sodium as disinfectant instead of formaldehyde, and after verifying complete wash-out of precipitated formaldehyde, hemodialysis with volunteered patients was done, which uneventfully continued to the end. It became evident that the use of outdated formaldehyde for disinfecting hemodialysis machines and its precipitation in pipelines and connectors of machines was the cause of high-grade fever, chills, generalized pruritus, and occasionally increased blood pressure in our patients.

*Dialyzer reaction* is the term for a broad group of events that include both anaphylactic and less well-defined adverse reactions of unknown cause. In the past, many of these reactions were grouped under the term “first use” syndrome, because they presented much more often when new (as opposed to reused) dialyzers were employed. However, similar reactions occur with reused dialyzers, and adverse reactions are now discussed under the more general categories of anaphylactic type (type A) and nonspecific type (type B).<sup>1,2</sup> When a full-blown severe type A reaction occurs manifestations are those of anaphylaxis. Common presenting symptoms are dyspnea, a sense of impending doom, and a feeling of wrath at the fistula site or throughout the body. Cardiac arrest and sudden death may supervene. Milder cases may present only with itching, urticaria, cough, sneezing, coryza, or watery eyes. The signs and symptoms in our patients were only high-grade fever, chills, pruritus, and occasionally elevated blood pressure. Patients with a history of atopy and/or with eosinophilia are prone to develop these reactions. In our patients, there was no history of atopy or allergy, and the

symptoms began during the first few minutes, maximally within 30 minutes of dialysis, which is compatible with type A reactions. Ethylene oxide as the cause of symptoms in our patients was ruled out, because the patients had the same symptoms with gamma-irradiated filters or reused filters, and there was no eosinophilia in the patients.<sup>3</sup> We were using polysulfone filters at that time. In addition, the symptoms continued after discontinuation of angiotensin-converting enzyme inhibitors and all other drugs. These facts rule out the possibility of reaction to polyacrylonitrile-based membrane.<sup>4,5</sup>

Contaminated dialysate reaction usually begins in the early phase (within two minutes) of initiating dialysis, but fever and chills are also particularly common symptoms with these reactions.<sup>6</sup> Nonetheless, negative results of multiple cultures and the use of the same dialysis solution in other hemodialysis centers with no dire consequences, exonerated the dialysis solution. Allergic reaction to heparin is most unlikely too, regarding sudden onset of symptoms in all 50 patients and the persistence of symptoms after using heparin-free hemodialysis.

Formaldehyde (oxidized methanal) is the chemical compound with the formula  $H_2CO$ . The simplest aldehyde, an aqueous solution of formaldehyde can be useful as a disinfectant as it kills most bacteria and fungi (including their spores). It is also used as a preservative in vaccination.<sup>7</sup> Formaldehyde can be toxic, allergenic, and even carcinogenic. Formaldehyde toxicity resulting from improper disinfectant use and leaching from sediment filters has caused hemolytic anemia and death.<sup>7</sup> In our patients, the history, signs and symptoms, and chronology is compatible with allergic reaction to outdated formaldehyde. Patients undergoing long-term hemodialysis are often exposed to formaldehyde, and it has been reported to cause immunoglobulin E (IgE)-mediated anaphylactic shock. In one study, formaldehyde was shown to cause symptoms in some patients under long-term hemodialysis, but an IgE-mediated mechanism was not demonstrated.<sup>8</sup> In another study, 106 unselected patients on long-term hemodialysis were screened for allergic symptoms, specific IgE against ethylene oxide, isocyanates, formaldehyde, phthalates, total IgE, and eosinophil count. The study confirmed the role of specific IgE against ethylene oxide, but not of the other dialysis materials in the allergic

sensitization.<sup>9</sup> In another study, by using an in vitro test, the presence of formaldehyde-specific IgE antibodies was investigated in sera from 4 groups of individuals exposed to formaldehyde by different routes and concentrations, one group consisting of patients on long-term hemodialysis.<sup>10</sup> It was concluded that exposure to formaldehyde, even in relatively high concentrations, rarely evokes production of specific IgE antibodies. The presence of these specific antibodies is not necessarily attended by allergic symptoms. On the other hand, the symptoms supposed to be related to formaldehyde exposure and reported in that study could not be attributed to an IgE-mediated sensitization to formaldehyde, at least in some patients.<sup>10</sup> We were not able to measure formaldehyde-specific IgE antibodies in our patients, but symptoms and signs, sequence of the events, and termination of all sign and symptoms after replacing formaldehyde by sodium hypochlorite are strongly suggestive that outdated formaldehyde was the culprit.

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