Intravenous Fluid Contamination, Aegean-Style

You can imagine my surprise when I first read the paper by Matsaniotis et al, which appears in this issue of Infection Control. I was stunned. Here, a full decade after onset, with high fever, rigors, hypotension, and abdominal classic indicators were present. Large numbers of the problem. From the epidemic curve, it appears that colleagues in Greece, it is possible to portray the full scope of the problem. From the same all-too-familiar characters — *Enterobacter agglomerans* and *E. cloacae*, the screw-top bottle, the relatively low-risk patients with sudden nosocomial gram-negative sepsis, the baffled clinicians, the delayed recognition of the cause of the problem, the tardy recall. Somehow this Aegean drama passed virtually unnoticed in the US until the report from the Aghia Sophia Children’s Hospital in Athens reached this Journal. It is a fascinating story, deserving of careful study.

Based on the manuscript and correspondence with colleagues in Greece, it is possible to portray the full scope of the problem. From the epidemic curve, it appears that the outbreak of enterobacter bacteremia may have started as early as January 1981. Physicians at the Aghia Sophia Hospital first suspected an outbreak in March, and by April it was clear that an epidemic was in progress. There was abundant evidence to suggest that contaminated fluid was at the root of the problem. Indeed, virtually all of the classic indicators were present. Large numbers of patients who were not particularly high risk for nosocomial sepsis abruptly became ill. The precipitous onset, with high fever, rigors, hypotension, and abdominal signs, was highly suggestive of gram-negative bacteremia, and there was no obvious source of infection other than the intravenous infusion system. Discontinuation of the infusion resulted in prompt clinical improvement in almost all cases. The pathogens recovered from blood cultures, *E. agglomerans* and *E. cloacae*, are both well known for their ability to proliferate in dextrose-containing intravenous fluids, and both were implicated in the nationwide epidemic in the US. Finally, all of the isolates of each enterobacter species had the same antibiogram. In the case of *E. agglomerans*, the strain was susceptible to many first-line antibiotics, which suggested that it was not a typical endemic nosocomial pathogen.

Although the physicians at Aghia Sophia were undoubtedly aware of these danger signals, their initial inability to recover *Enterobacter* from unopened IV bottles apparently made them reluctant to accept the epidemiological facts at face value. Rather than aggressively pursuing the possibility of intrinsic intravenous fluid contamination — perhaps even requesting a recall — they attempted to contain the problem through traditional infection control interventions, such as handwashing before cannula insertion and careful preparation of the IV site. These measures were undoubtedly aimed at preventing cannula-related bacteremia, and it is possible that the investigators were influenced by American data indicating that fluid contamination is a far less frequent source of bacteremia than cannula infection. At any rate, Matsaniotis and his colleagues hedged their bets. They instituted 24-hour changes of IV administration systems, a strategy that had reduced the level of organisms in the infusate and the severity of the infections in the American epidemic.

These infection control measures at first seemed to have the desired effect, as the number of cases fell in May. However, the infection rate increased abruptly in June and July, providing additional evidence that contaminated fluid was to blame. By then, extensive microbiological investigation had revealed that the tops of the IV bottles were heavily contaminated with a number of pathogens, including *Enterobacter*, and that these bacteria could gain access to the IV fluid during assembly of the administration system. On July 24, the National Ministry of Health was notified. Reports from other institutions also began to reach the health authorities at about the same time. The story exploded in the newspapers a few days later (Figure). “Stop immediately the use of dextrose IV fluids” was the banner headline in the largest circulation daily. Other papers lead with, “Lethal IV fluids are in use in Greece,” and “Big scandal with the IV fluids.” A recall was demanded by the government, but it was limited only to 5% dextrose fluids of the implicated manufacturer, Chropei. The epidemic continued to smolder. An official committee of inquiry was set up by the government, but there have been allegations that the investigation was desultory, in part because Chropei was the only Greek manufacturer of IV fluids, and a complete recall or plant closure would have necessitated importation of vast quantities of IV products. Moreover, there are indications
that a thorough microbiological investigation of the plant may have been resisted. Approximately 2 months after the recall, the government issued assurances that the Chropei product was now sterile. Within one week of its reintroduction at Aghia Sophia, seven cases of enterobacter bacteremia were documented. Cultures of the manufacturing plant environment revealed extensive contamination with Enterobacter, and all IV products were recalled. Chropei was eventually nationalized.

This was an epidemic of extraordinary dimensions. Sixty-three cases were documented in a single 500-bed pediatric hospital, and the authors remark that many other cases of apparent primary bacteremia occurred but were not cultured because the housestaff adopted the habit of just discontinuing the IV when a patient spiked a fever. Since the manufacturers had a virtual monopoly on IV fluid distribution in Greece, it is likely that hundreds, probably thousands, of cases occurred. This epidemic was almost certainly far larger than the 1970 to 1971 American epidemic in which 397 cases occurred in the 25 hospitals that were investigated.

In retrospect, it appears that the Greek intravenous fluid industry and regulatory agencies simply failed to learn from American experience. In the US, the events of 1970 to 1971 led to discontinuation of screw-cap closures for intravenous fluids and increased emphasis on the control of environmental contamination in manufacturing facilities. There was also considerable discussion concerning microbiological sampling of intravenous products before shipment as a final sterility check, although few changes in microbiological quality control were actually implemented. But the most important result of the American outbreak was the sudden realization by both industry and the consumer that an epidemic of such magnitude actually could occur. The infection control community has been vigilant ever since, and even a single case of unexplained enterobacter septicemia prompts an American hospital epidemiologist to entertain at least the possibility of intravenous fluid contamination. Today, bacteremia caused by an organism known to multiply in intravenous fluid undoubtedly would lead to a similar level of concern in Greece.

The work of Matsaniotis et al. reveals a high level of sophistication in microbiology and infection control. One cannot help but wonder whether a similar episode in a country without substantial microbiological and epidemiological resources would be identified as quickly, if at all. Intravenous fluid contamination is not confined to Europe and North America. Unfortunately, the risk of contamination due to poor manufacturing practices and inadequate quality control is probably greatest in areas of the world where epidemic intravenous-associated sepsis is least likely to be recognized.

REFERENCES


