

## In-Use Contamination of Intravenous Infusion Fluid

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During the 1970 to 1971 nationwide epidemic of septicemias caused by *Enterobacter cloacae* and *Enterobacter agglomerans* traced to intrinsic contamination of Abbott intravenous infusion products, 94 infusion systems manufactured by Baxter Laboratories were studied microbiologically and epidemiologically during hospital use. Intravenous fluid from 10 systems (11%) contained microorganisms, usually *Staphylococcus* or *Bacillus* species; one infusion was heavily contaminated with *Klebsiella pneumoniae*. No national epidemic organisms, *E. cloacae* or *E. agglomerans* (formerly *Erwinia*), were recovered, suggesting that during this period frequent contamination with these organisms was unique to Abbott's infusion products. Contamination in this study appeared to be extrinsic in origin (introduced during clinical use) and related to the duration of continuous intravenous therapy. Nine of 61 systems (15%) that had been used longer than 48 h were contaminated, whereas only 1 of 33 used less than 48 h (3%) contained microorganisms. This study and the recent national outbreak indicate that contamination of infusion fluid, both from intrinsic and extrinsic sources, must be recognized as an additional risk of intravenous therapy; however, a once-daily replacement of the delivery apparatus can significantly diminish this hazard.

Between summer 1970 and March 1971, many U.S. hospitals experienced outbreaks of intravenous (i.v.)-associated septicemia with *Enterobacter cloacae* and *Enterobacter agglomerans*, ultimately traced by the Center for Disease Control to intrinsic contamination of infusion products manufactured by Abbott Laboratories (7, 12, 16, 17; E. J. Fisher, D. G. Maki, J. Eisses, T. R. Neblett, and E. L. Quinn, Progr. Abstr. Intersci. Conf. Antimicrob. Ag. Chemother., 11th, Atlantic City, N. J., p. 20, 1971). *E. agglomerans*, formerly designated *Erwinia* (11), a member of the *herbicola-lathyri* group and more commonly known as a plant-associated bacterium, had been an uncommon human pathogen in the past and rarely isolated from blood (27, 29). In early 1970, Abbott introduced into use a new, Elastomer-lined screw-cap closure for i.v. bottles. Over 40% of cap assemblies from several thousand bottles of warehouse stock sampled were found to contain microbial contamination with a large variety of organisms, including the epidemic strains *E. cloacae* and *E. agglomerans* (7, 17; D. C. Mackel, D. G. Maki, R. A. Anderson, F. S. Rhame, and J. V. Bennett, Progr. Abstr. Intersci. Conf. Antimicrob. Ag. Chemother., 11th, Atlantic City,

N.J., p. 20, 1971). Culture surveys of Abbott i.v. systems during clinical use in two hospitals during the epidemic had disclosed up to 25% rates of fluid contamination; *E. cloacae* and *E. agglomerans* were recovered from multiple infusions (17). In January and February 1971, before the source of contamination of Abbott's fluids was identified as intrinsic, present within the system from its manufacture, culture studies of other manufacturers' i.v. fluids were undertaken to (i) find if epidemic organisms *E. cloacae* and *E. agglomerans* were also present in infusion products other than Abbott's sampled during hospital use, (ii) determine the magnitude of in-use contamination of i.v. fluid in hospitals which did not use Abbott infusion products and also had not experienced outbreaks, and (iii) gain knowledge of the epidemiologic variables influencing contamination. (This study was presented in part at the Annual Meeting of the American Society for Microbiology, Minneapolis, Minn., May, 1971.)

### MATERIALS AND METHODS

**Background.** The institution selected for study, Grady Memorial Hospital, is a 1,500-bed acute care municipal hospital located in downtown Atlanta, Ga., and is staffed by house officers and faculty from Emory University School of Medicine. Its Infections Committee conducts periodic prevalence surveys of

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nosocomial infection (1). Outbreaks or even isolated instances of septicemia attributable to contaminated infusion fluid have not been detected. At the time of the study, infusion products manufactured by Baxter Laboratories had been used exclusively for 10 years. Parenteral products were delivered to the hospital, stored in central supply, and delivered to patient care units on a weekly basis. All devices for venous cannulation, both steel needles and plastic catheters, were inserted by ungloved house officers or medical students after cutaneous disinfection with 70% alcohol or an iodophor. Thereafter, the nursing staff provided all maintenance care of i.v. infusions, with the exception of direct i.v. injections of medications. No formal protocol or other written policy governed insertion of i.v. cannulae or day-to-day management of i.v. therapy. As in virtually all American hospitals at that time (7, 16), administration sets were not routinely replaced, including when the cannula was changed; replacement usually only followed frank malfunction such as leakage or impeded flow. Also, no specific precautions such as gloves or application of disinfectants to the delivery apparatus were employed during initial set-up and subsequent manipulation of infusion systems.

**Epidemiologic methods.** Five general medical wards, each with an attached intensive care unit, four surgical wards, and the pediatric unit were selected for study. Over a 3-day period in January 1971 each of the wards was visited at least once, making an attempt to culture every available i.v. infusion on the ward. For each infusion, the specific types of bottles, solutions, administration sets, volume-control reservoirs, connectors, stopcocks, manometers, and other equipment constituting the delivery apparatus were noted; the entire system was inspected for evidence of malfunction, particularly leakage or inadequacy of interposed equipment, gross contamination, blood, particulate matter, or turbidity within the fluid. The infusion site was uncovered, and the type of cannula and any malfunction such as infiltration or leakage was recorded. The site was carefully examined for evidence of inflammation (phlebitis). Phlebitis was defined as the presence of two or more of the following: erythema, increased warmth, tenderness to palpation extending beyond the cannula tip, edema, or a palpable cord. In addition, the lengths of time that the current cannula had been in place and the sampled i.v. bottle had been hanging and how long the patient had received continuous, uninterrupted i.v. therapy were obtained from the nurse's label on the bottle, the patient record, or direct inquiry of the ward nurses. All i.v. medications, both added directly to the bottle (additives) or injected into the infusion line, were recorded. All clinically recognizable or culture-proven infections, any potential sites of infection, such as urethral catheterization or intratracheal intubation, and all major medical diagnoses were noted.

**Microbiology.** After inspection, the entire delivery apparatus was removed for sampling when 200 ml or less remained within the bottle. When two bottles fed the same infusion site (a dual system), the administration set that had been in longest continuous use

was sampled. The bottle and administration set were removed in toto, and a sterile cap was placed over the distal end of the administration set tubing. It was not logistically possible to remove and culture cannulae as part of this study. The bottle and attached administration set were immediately transported to the laboratory in a sterile plastic bag for microbiological sampling. Approximately two-thirds of the systems were sampled in a laminar flow hood at the Center for Disease Control and the remaining one-third in a quiet, minimally occupied laboratory within the hospital.

For sampling of fluid (2; Mackel et al., *Progr. Abstr. Intersci. Conf. Antimicrob. Ag. Chemother.*, 11th, Atlantic City, N.J., p. 20, 1971), the sterile cap was removed from the distal end of the administration set tubing, and the end was flamed and attached to a bacteriological field monitor (Millipore Corp.; mean pore size 0.45  $\mu$ m). The 10- to 12-ml contents of the administration set were filtered under negative pressure through the monitor. If antimicrobial agents had been administered through the set, after filtration of i.v. fluid, the membrane filter was washed by filtering 100 ml of sterile 0.9% saline. The filter was removed from the plastic holder and placed aseptically onto a plate of Trypticase soy agar containing 5.0% sheep's blood, which had been premoistened with 0.2 ml of brain heart infusion broth enriched with 0.5% beef extract. After incubation at 37 C for 72 h, all morphological colony types present were subcultured and microbiologically identified by methods and criteria in use at the Center for Disease Control. Plates negative for growth at 72 h were further incubated at 25 C for 5 days before discarding. The entire contents of 50 500- and 1,000-ml unopened bottles of fluid, randomly selected from the study wards, were samples in a similar manner. Also, 50 administration sets from hospital stock were cultured by infusing enriched brain heart infusion broth through the set and incubating the broth at 37 C for 48 h.

## RESULTS

During the 3-day periods, 94 infusions from 89 patients were microbiologically sampled. Fluid from the administration set of 10 (11%) yielded microbial contaminants (Table 1). No patient became septicemic with organisms similar to those isolated from his infusion. Contamination rates were comparable among medical and surgical patients; no pediatric i.v. systems were found contaminated, although only nine were sampled. No clustering of contaminated infusions by ward, day of study, location of sampling (hospital laboratory or Center for Disease Control), or product lot number was observed.

As seen in Table 2, staphylococci, *Staphylococcus epidermidis* or *Staphylococcus aureus*, were isolated from 8 of the 10 positive systems; *Escherichia coli* and *Klebsiella pneumoniae* were each recovered from one infusion. Only the infusion containing *K. pneumoniae* was heavily

contaminated, i.e., confluent growth on the membrane filter, indicating a level of contamination exceeding 30 organisms per ml. All of the other positive systems yielded only very low numbers of organisms, ranging from one to six per administration set. Cultures of the 50 unopened bottles and unused administration sets were negative for microbial growth.

Severity of underlying illness, age, or sex did not influence contamination. Table 3 lists some of the clinical variables which were analyzed seeking an epidemiologic association with contamination of fluid. Peripheral sites of infection, fever, bottle additives or i.v. medications, antibiotics (i.v. or non-i.v. route), type of i.v. fluid, and type of cannula showed no correlation. Phlebitis, malfunction of the infusion apparatus, and interposition of a three-way stopcock into the infusion line were all consider-

ably more frequent in contaminated systems. Over two-thirds of study patients had active or previously active peripheral infections which did not appear to influence the microbiological status of their infusion, with the exception of the two patients with gram-negative bacillus contamination of fluid who both had previous peripheral infections with organisms taxonomically similar to those subsequently isolated from their i.v. fluid. Unfortunately, the isolates from these infections were not available for subtyping and comparison with the strains isolated from fluid. The mean number of hours that bottles of sampled systems had been hanging and of continuous venous cannulation did not differ significantly between contaminated and noncontaminated systems. However, the mean duration of uninterrupted infusion in contaminated systems, 5.3 days, significantly exceeded that of noncontaminated systems, 3.7 days ( $P < 0.05$ ). Only 1 of 33 systems (3%) in continuous use less than 48 h contained micro-

TABLE 1. Prevalence of contaminated infusion fluid and phlebitis<sup>a</sup>

Specialty service	No. of infusions	No. with contaminated fluid	No. with phlebitis
Medicine .....	66	8 (12)	18 (30)
Surgery .....	19	2 (11)	11 (58)
Pediatrics .....	9	0	0

<sup>a</sup> The presence of phlebitis could not be evaluated in seven patients. Numbers in parentheses indicate percentage.

TABLE 2. Microbiologic profile of contaminated i.v. fluid

Study no.	Organisms cultured <sup>a</sup>	Count (per 10 ml)
3	Coagulase-neg. <i>S. aureus</i> <sup>b</sup>	1
10	Coagulase-neg. <i>S. aureus</i> (1) <sup>c</sup> <i>S. epidermidis</i> (1) <i>Bacillus</i> spp. (3)	5
13	Coagulase-neg. <i>S. aureus</i>	1
20	Coagulase-pos. <i>S. aureus</i>	17
26	Coagulase-neg. <i>S. aureus</i>	1
33	Coagulase-neg. <i>S. aureus</i>	1
55	<i>S. epidermidis</i>	1
59	<i>E. coli</i>	4
65	<i>Klebsiella pneumoniae</i>	TNTC <sup>d</sup>
68	<i>S. epidermidis</i> (5) Micrococcus (1)	6

<sup>a</sup> By Millipore filtration.

<sup>b</sup> Anerobic fermentation of 1% mannitol and pigment production (4, 6).

<sup>c</sup> Number of organisms of each isolate (in parentheses) in instances of mixed contamination.

<sup>d</sup> TNTC, Too numerous to count; confluent growth on Millipore filter.

TABLE 3. Epidemiologic features of intravenous infusions studied

Feature	No. of systems noncontaminated <sup>a</sup>	No. of systems contaminated <sup>a</sup>
Infusion sampled .....	84	10
Peripheral site of infection .....	58 (69)	7 (70)
Fever (>101 F) .....	23 (28)	3 (30)
Phlebitis .....	24 (29)	5 (50)
Additives in bottle .....	57 (68)	5 (50)
Antibiotics		
i.v. ....	42 (50)	5 (50)
Any route .....	54 (64)	7 (70)
Glucose-containing fluid .....	73 (87)	9 (90)
System malfunction .....	29 (35)	5 (50)
Three-way stopcock .....	47 (56)	8 (80)
Cannulae		
Scalp vein needle .....	20 (24)	3 (30)
Plastic catheter .....	55 (65)	7 (70)
Central venous pressure catheter .....	8 (10)	0
Duration ± SEM <sup>b</sup>		
Bottle (h) .....	13.0 ± 1.3	15.7 ± 4.6
Cannula (h) .....	40.8 ± 3.2	53.9 ± 8.1
Continuous i.v. therapy (days) .....	3.7 ± 0.3	5.3 ± 1.3 <sup>c</sup>

<sup>a</sup> Total at risk for some of the variables is less than the total number of infusions sampled. Numbers in parentheses indicate percentage.

<sup>b</sup> SEM, Standard error of the mean.

<sup>c</sup>  $P < 0.05$ .

organisms, whereas 9 of 61 (15%) which had infused for more than 48 h were colonized (Table 4;  $P = 0.063$ ).

Infusion phlebitis could be assessed in 87 infusions (Table 5). Phlebitis, present in 29 (32%), did not correlate with the type of i.v. solution administered, system malfunction, contamination of fluid, or i.v. medications, with the exception of antibiotics. Phlebitis accompanied 42% of all antibiotic infusions, usually of penicillin, cephalothin, ampicillin, or nafcillin, whereas only 22% of infusions without i.v. antibiotics led to phlebitis ( $P < 0.05$ ). Type of venous cannula also significantly influenced phlebitis: no phlebitis was noted in 23 patients receiving infusion therapy through scalp vein needles, whereas phlebitis was present in 29 (45%) of 64 patients receiving fluids through plastic catheters ( $P < 0.001$ ). With plastic catheters, the rate of phlebitis was correlated strongly with the duration of cannulation; phle-

bitis complicated 76% of catheterizations exceeding 48 h and only 26% of those less than 48 h ( $P < 0.005$ ). The prevalence of phlebitis on the surgical service, 58%, considerably exceeded that on medicine, 30%; however, only 1 of 19 surgical infusions employed scalp vein needles, whereas these devices were used in one-fourth of medical infusions. With infusions through plastic catheters, the rates of phlebitis on the two services were similar.

## DISCUSSION

No epidemic organisms, *E. cloacae* or *E. agglomerans*, were isolated from the 94 infusions of Baxter i.v. products sampled during clinical use. Three comparable surveys of Abbott products in two hospitals between December 1970 and February 1971 showed 17 to 25% rates of in-use contamination and 2 to 5% positivity for the epidemic strains (17). Thus, it appeared, based upon this sample, that during this period, i.v. fluid contamination with *E. cloacae* and *E. agglomerans* was much more frequent with Abbott's products. This conclusion was further substantiated by a prospective comparative study of in-use Abbott and Cutter infusion products within a single hospital (17). Although initial culture surveys of unused Abbott fluids had been inconclusive (7, 17; Fisher et al., Progr. Abstr. Intersci. Conf. Antimicrob. Ag. Chemother., 11th, Atlantic City, N.J., p. 20, 1971), the seeming absence of epidemic organisms in the infusion products of two other major manufacturers during that period was a major influence in directing an even more exhaustive and ultimately successful search for an intrinsic source of Abbott fluid contaminants.

The observed prevalence of in-use contamination in this study, 11%, is impressively high and would probably have been even higher had the entire fluid contents of each infusion been sampled, i.e., fluid within the bottle as well as administration set and both halves of dual infusions. Negative cultures of unused fluids and delivery apparatus suggests that the source of contamination was extrinsic, i.e., microorganisms were introduced into the infusion during or after setup for use and also were unlikely to have been a consequence of the sampling process.

Contamination of infusion fluid from extrinsic sources has very likely caused sporadic septicemias for as long as i.v. therapy has been employed (10, 16, 18, 24, 25); however, such infections have for the most part remained unrecognized or have been attributed to the can-

TABLE 4. Relationship of duration of infusion therapy and in-use contamination of infusion fluid

Continuous infusion therapy (h)	No. of systems at risk	No. with fluid contamination <sup>a</sup>
≤48	33	1 (3)
>48	61	9 (15) <sup>b</sup>

<sup>a</sup> Numbers in parentheses indicate percentage.

<sup>b</sup>  $P = 0.063$  by Fischer's exact test.

TABLE 5. Relationship of type of cannula, duration of cannula placement, and intravenous antibiotics to infusion phlebitis

Factor <sup>a</sup>	No. of systems at risk <sup>b</sup>	No. with phlebitis <sup>c</sup>	<i>P</i> value <sup>d</sup>
Cannula			
PC	64	29 (45)	<0.001
SVN	23	0	
PC placement			
24 h	18	0	<0.005
25 to 48 h	21	10 (48)	
>48 h	25	19 (76)	
i.v. antibiotics			
No	40	9 (22)	<0.05
Yes	47	20 (42)	

<sup>a</sup> PC, Plastic catheter; SVN, scalp vein needle.

<sup>b</sup> Phlebitis could not be assessed in seven systems.

<sup>c</sup> Presence of two or more of following: palpable cord, local tenderness, heat, redness, or edema. Numbers in parentheses indicate percentage.

<sup>d</sup> By Fischer's exact test or chi-square test with Yates correction.

nula. Wilmore and Dudrick reported seven contaminated systems of 220 in a study of in-line Millipore filters, but did not report microbiological identities or quantitative levels of contamination (30). Deeb found that 3.8% of 236 in-use bottles of conventional i.v. solution contained microorganisms, most likely of extrinsic origin (9), and Duma et al., in July 1970, identified four septicemias related to in-use contamination of infusion fluid and discovered that 35% of in-use i.v. administration sets in their hospital were contaminated, many with more than one organism (10). However, Abbott fluids were used in this latter study, and it is impossible to assess the extent to which the results might have been influenced by unidentified intrinsic contamination. In both of the aforementioned studies, quantitative sampling methods were not employed. In a university hospital investigation, in February 1971, we recovered microbial contaminants from 6.8% of 148 Cutter systems sampled during clinical use; the profile of contamination, both microbiologically and quantitatively, was similar to that found in this study (17). In that study as in this one, contaminants appeared to be of extrinsic origin, related to the many manipulations of infusion apparatus which occur in the course of i.v. therapy, such as attachments of the administration set, addition of medications to the bottle, injections into the tubing, manometric measurements, and handling of the cannula. Three independent studies of commercial infusion fluid which was cultured immediately after introduction of additives in the hospital pharmacy, but before delivery to patient care units, found 3.0 to 17.7% rates of contamination (3, 19; L. J. Hak, J. L. Long, R. L. Ruberg, and H. L. Flack, Annu. Meet. Amer. Soc. Hosp. Pharm., 1971). Our experience and all of these studies, and the growing number of reported outbreaks of infusion-related sepsis (7, 8, 10, 12, 22, 25; Fisher et al., Progr. Abstr. Intersci. Conf. Antimicrob. Ag. Chemother., 11th, Atlantic City, N.J., p. 20, 1971; Report of the committee appointed to inquire into the circumstances, including the production, which led to the use of contaminated infusion fluids in the Davenport Section of Plymouth General Hospital, Her Majesty's Stationery Office, London, 1972), strongly emphasize that contamination of infusion fluid, especially from extrinsic sources, is relatively common and now must be recognized as an additional hazard of i.v. therapy.

Intravenous systems in continuous use beyond 48 h incurred a considerably greater risk of contamination, 15% (Table 4), suggesting that the risk of introduced contamination is

cumulative. It is noteworthy that this critical interval of uninterrupted infusion, beyond which contamination rises sharply, is identical to the critical period which has been statistically established by multiple independent studies for catheter-tip contamination and catheter-related sepsis (16). Michael and Ruebner first demonstrated (18), and we have confirmed, that microorganisms capable of growing in infusion fluid, once introduced into an in-use system, can perpetuate in the administration set for many days despite serial replacements of the bottle and high rates of fluid flow (16, 17). In this country in the past, administration sets have not been routinely changed and have usually been replaced only when they malfunctioned or became sufficiently dirty to become aesthetically offensive.

Organisms recovered from in-use fluid, especially *Staphylococcus* and *Bacillus* species, are recognized skin commensals. Gram-negative organisms have been recovered with high frequency from the skin of patients (23) and from the hands of up to 40% of hospital personnel randomly sampled (26). An outbreak of five *Klebsiella pneumoniae* i.v.-associated septicemias in an intensive care unit was linked to contaminated nurses' hand lotions (21). In our study, peripheral infections with organisms taxonomically similar to strains later isolated from infusion fluid twice preceded in-use fluid contamination and suggests an increased risk of i.v.-fluid-related infection in patients with an established active infection. Such a hazard has been confirmed with catheter-associated sepsis (5, 20). Manual contact with the infusion apparatus by medical personnel is probably the major mechanism of microbial ingress to fluid and possibly even the cannula wound (16). The urgent necessity for frequent hand washing by physicians and nurses cannot be emphasized too strongly.

The fact that the only heavily contaminated infusion among the 10 culture-positive systems yielded *K. pneumoniae* is not unexpected. *Enterobacter* species and to a lesser extent *Klebsiella* and *Serratia*, all members of the tribe *Klebsielleae*, predominated in the recent national outbreak (7, 12; Fisher et al., Progr. Abstr. Intersci. Conf. Antimicrob. Ag. Chemother., 11th, Atlantic City, N.J., p. 20, 1971), and also in other reports of sepsis traced to contaminated fluid (10, 18, 25). We have found that members of this tribe possess a selective ability over other more common nosocomial pathogens to proliferate in glucose-containing i.v. solutions at room temperature (17). Fifty-one strains, twice-washed to remove organic nutri-

ents, inoculated into 5% dextrose-in-water and incubated at 25 C attained a mean 24-h concentration of over  $10^5$  organisms per ml. In contrast, 50 of 51 clinical isolates of *Staphylococcus*, *Pseudomonas*, *Proteus*, *Escherichia*, and *Herellea* did not grow or more commonly died. These studies have subsequently been confirmed by other investigators (12, 13, 14). Thus, in septicemias suspected to be due to contamination of infusion fluid, infection with one or more members of tribe *Klebsiellae* should be expected and, after discontinuing the infusion, antimicrobial therapy, when clinically indicated, should be chosen for bactericidal activity against these organisms.

Realizing a cumulative risk of in-use contamination of fluid, which increases significantly after 48 h of continuous infusion, and the ability of many common hospital pathogens in fluid to amplify contamination logarithmically within 24 h, it is recommended that all infusion apparatus down to the cannula (bottles and administration sets) be routinely changed every 24 h, and at each change of cannula, all equipment be totally replaced. Several hospitals instituting this control measure in the recent national outbreak noted decreased epidemic septicemias (7, 12, 16, 17; Fisher et al., Progr. Abstr. Intersci. Conf. Antimicrob. Ag. Chemother., 11th, Atlantic City, N.J., p. 20, 1971). The efficacy of this simple measure in diminishing infections consequent to intrinsic contamination of fluid augurs for its consideration to prevent infections caused by extrinsically introduced organisms.

The higher frequencies in this study of phlebitis in patients cannulated over 48 h, with plastic i.v. catheters, and receiving i.v. antimicrobial agents known to cause venous inflammation, are in accord with previous epidemiologic studies of infusion phlebitis (15, 28). A relationship between microbial contamination of fluid and phlebitis was not demonstrated, possibly because of the limited number of systems sampled. However, during the national epidemic, we found that in septicemias due to contaminated fluid, infusion phlebitis, often disproportionately severe, was present in 50% of cases; patients briefly cannulated, for less than 24 h and in many instances only with steel needles, suffered severe phlebitis (7, 16, 17).

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