JOURNAL OF CLINICAL MICROBIOLOGY, Mar. 1985, p. 357–360
0095-1137/85/030357-04$02.00/0

Vol. 21, No. 3

Pathogenesis of Catheter Sepsis: a Prospective Study with Quantitative and Semiquantitative Cultures of Catheter Hub and Segments

JOSEFINA LIÑARES,[1]* ANTONIO SITGES-SERRA,[2] JAVIER GARAU,[3] JOSÉ L. PÉREZ,[1] AND ROGELIO MARTÍN[1]

Service of Microbiology,[1] Department of Surgery,[2] and Infectious Diseases Unit,[3] Hospital "Principes de España," Hospitalet de Llobregat, Barcelona, Spain

Received 16 August 1984/Accepted 4 December 1984

Our purpose was to study prospectively the causes, routes of infection, and frequency of catheter-related sepsis in patients on total parenteral nutrition. From January 1981 to January 1984, cultures of 135 subclavian catheters from 135 adult patients were done by quantitative and semiquantitative methods. Twenty patients (14.8%) had catheter-related sepsis. Fourteen episodes (70%) stemmed from an colonized hub. Skin infection (*Staphylococcus aureus*, 2 cases), total parenteral nutrition mixture contamination (*Enterobacter cloacae*, 2 cases), and hematogenous seeding of the catheter tip (*Yersinia enterocolitica*, 1 case, and *Streptococcus faecalis*, 1 case) accounted for the remaining six septic episodes. The catheter hub is, in our experience, the most common site of origin of organisms causing catheter tip infection and bacteremia.

Catheter-related sepsis (CRS) is a well-known complication of total parenteral nutrition (TPN) therapy (16, 19, 23, 24). In recent studies the incidence of CRS ranges from 7 to 42% (2–4, 7, 8, 13, 24). Microbial infection of intravascular inserts results from invasion of organisms present at the insertion site, contaminated infusate, hematogenous seeding of the catheter tip, and contamination of catheter hub (16, 24). The purpose of this study was to determine the routes of infection in 20 cases of CRS and to assess the usefulness of quantitative (Q) and semiquantitative (SQ) culture techniques to clarify the pathogenesis of CRS.

MATERIALS AND METHODS

During a 3-year period (January 1981 to January 1984) 135 subclavian catheters were prospectively studied. For 20 catheters (14.8%) the culture yielded the same microorganism that was recovered from blood. These 20 cases of CRS form the basis of this study. All catheters were inserted in the operating room under strict aseptic conditions. They were used exclusively for TPN administration. TPN solutions were prepared in the Pharmacy Department of this institution under a laminar flow hood. In febrile patients with suspected CRS, two sets of blood cultures were obtained from peripheral veins, the catheter was aseptically removed, and three segments (Fig. 1) were immediately sent in sterile containers to the laboratory for culture: (i) a subcutaneous 3-cm-long segment beginning several millimeters inside the former skin catheter interface, (ii) a intravascular (tip) 3-cm-long segment, and (iii) the hub. At the time of catheter removal, a swab was taken from the skin surrounding the puncture site, and a sample of 10 ml of TPN mixture was withdrawn and sent to laboratory for culture.

Microbiological studies. Blood cultures were performed by conventional methods. The swabs from skin were cultured on blood agar and Trypticase soy broth (TSB; BBL Microbiology Systems, Cockeysville, Md.). A 10-ml sample of TPN mixture was cultured in 10 ml of brain heart infusion broth and incubated at 35°C for 7 days before being discarded (17). Catheter cultures were performed by the SQ method proposed by Maki et al. (18) and by a modified Q method described by Cleri et al. (6). In the SQ method, each catheter segment was transferred to the surface of a 90-mm blood agar plate and rolled back and forth across the surface at least four times. After this, the Q method was carried out by flushing the catheter lumen with 2 ml of TSB, which was then diluted 10-fold, and 0.1 ml of each dilution was streaked onto horse blood agar plates. Thus, the internal surface of each catheter segment was cultured by the Q method, and the external surface was cultured by the SQ technique. Finally, the whole segment was immersed in 5 ml of TSB. Colonies were counted after 48 to 72 h of incubation. The catheter hub was cultured only by the quantitative method; bacterial and fungal isolates were identified by standard methods. Coagulase-negative staphylococci were speciated according to the method described by Kloos and Smith (14). Antibiotic susceptibility studies were performed by the disk diffusion method (1) and by the microdilution Sceptor System (BBL) (12).

The criterion for positivity with the Q method, it was $\geq 10^3$ CFU, and for the SQ method, it was ≥ 15 CFU.

CRS. The catheter was considered the source of sepsis when the same organism (identical biotype and susceptibility pattern) was isolated from the catheter tip and blood. This definition of CRS included the following.

(i) Hub-related sepsis. The same microorganism was recovered from hub, tip, and blood cultures. TPN mixture cultures were negative. Skin cultures were either negative or positive for different organisms.

(ii) Infusate-related sepsis. The same microorganism was present in the TPN mixture, hub, tip, and blood cultures. Skin cultures were negative.

(iii) Hematogenous seeding of the catheter. The same organism was isolated from blood, the catheter tip, and a distant source of infection, with negative TPN mixture, hub, and skin cultures.

(iv) Skin-related sepsis. The same microorganism was isolated from skin, the subcutaneous segment, the catheter tip, and blood, with negative hub and TPN mixture cultures.

* Corresponding author.

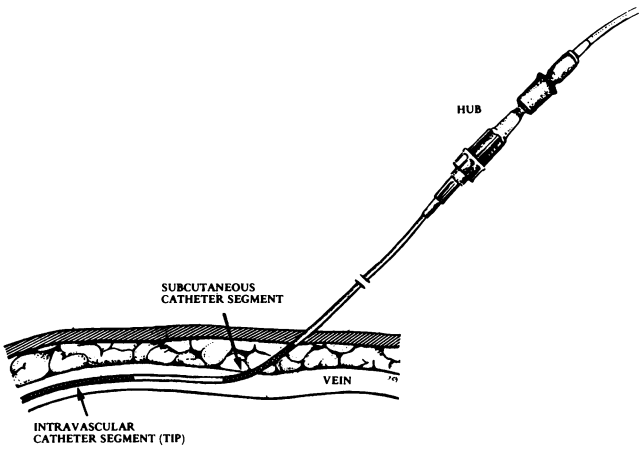

FIG. 1. Drawing of the three catheter segments for which cultures were done.

In all cases of CRS, tip cultures yielded >15 or $>10^3$ CFU with the SQ and Q methods, respectively.

RESULTS

CRS occurred in 20 instances. The systematic performance of TPN mixture, hub, catheter tip, skin, and blood cultures allowed us to recognize the origin the microorganisms causing sepsis. The results are shown in Table 1.

Hub-related sepsis. CRS in 14 patients (cases 1 through 14) was thought to originate from an colonized hub, with secondary colonization of the catheter tip and, finally, bacteremia. Catheter tips always yielded $>10^3$ CFU by the Q method, whereas the SQ technique only gave >15 CFU in 12 cases and yielded 7 CFU or no growth in the remaining two catheters. The Q culture of the subcutaneous segment gave $>10^3$ CFU in 10 instances, no growth in 2 cases, and $<5 \times 10^2$ CFU in 2 cases. The SQ culture yielded >15 CFU in eight cases and <15 CFU in three cases and was negative in three cases. Skin cultures were positive in three instances (21.4%): confluent growth of *Staphylococcus epidermidis* in one case <15 CFU of *Staphylococcus simulans* and *Staphylococcus haemolyticus* in two cases. These microorganisms were of different species and antibiotype than those recovered from the hub, tip, and subcutaneous catheter segments.

For all but one patient, cultures from other distant sites were negative. In case 13 the same bacteria (*Proteus mirabilis*) was recovered from a tracheostomy. In all cases TPN mixture cultures were negative. Excepting two instances (*P. mirabilis* and *Candida tropicalis*), all other hub-related sepsis were caused by coagulase-negative staphylococci.

Infusate-related sepsis. In cases 15 and 16, *Enterobacter cloacae* sepsis originated by contaminated infusate. In both cases, the tip, subcutaneous segment, and hub Q cultures yielded $>10^3$ CFU, whereas the SQ technique gave >15 CFU in each case for the tip but only in one case for the subcutaneous segment. Skin and other cultures were negative. Cultures of samples of TPN yielded *E. cloacae*.

Hematogenous seeding of catheter. In cases 17 and 18 the catheters were secondarily infected by hematogenous seeding from distant sites. In case 17, the catheter tip was colonized by *Streptococcus faecalis* coming from a urinary source, and in case 18 the tip was seeded by *Yersinia enterocolitica* in a patient with active Crohn's disease and multiple perianal fistulae. The Q and SQ cultures of the tips and subcutaneous segments were positive, whereas hub, TPN mixture, and skin cultures were sterile in both cases.

Skin-related sepsis. In two patients with *Staphylococcus aureus* sepsis, the skin, tip, and subcutaneous segment yielded confluent growth of *Staphylococcus aureus* by the SQ method. Only in case 19 was the culture positive by the Q method. In both cases, hub and TPN mixture cultures were negative. With SQ cultures we observed a gradient of colonization of the external surface of the catheter: in cases 1 through 18, the concentration of microorganisms was higher in the intravascular segment than in the subcutaneous segment; on the other hand, in the two cases of sepsis (numbers 19 and 20) caused by *Staphylococcus aureus* from an abscess at the catheter entry site, the skin and SQ subcutaneous segment cultures yielded heavier growth than did culture of the tip, strongly suggesting the direction of the advancing front of the spread.

DISCUSSION

CRS is one of the major complications of TPN therapy. It has been generally accepted that most CRS begin as a local infection of the skin at the entry site of the catheter (2, 13, 17, 18). Although this is true in some cases, typically in sepsis caused by *Staphylococcus aureus*, its importance has markedly decreased with improved catheter care, and other pathogenic mechanisms of infection are operative and are much more common than the catheter entry site infection. Thus, infusate contamination or hematogenous seeding of the catheter are other well-known pathogenic routes and are occasional causes of CRS (15–17). Epidemics of infusion-related sepsis are fortunately rare and are derived almost exclusively from infusate that has become contaminated during its manufacture or during preparation and administration in the hospital (15, 16). In our experience, two cases of catheter sepsis had this origin; both were caused by *E. cloacae*, a pathogen implicated in the majority of sepsis linked to contaminated fluid (17). Hematogenous seeding was responsible of CRS in cases 17 and 18 of our series. Another mechanism of CRS, the most frequent in our experience (21–24; A. Sitges-Serra, J. Liñares, and J. Garau, Surgery, in press) is catheter hub colonization, largely overlooked by most investigators up to the present time. In a previous report (24), we described an outbreak of coagulase-negative staphylococci CRS secondary to hub colonization due to its manipulation by nurses. Deitel et al. (7) had a very similar experience with an outbreak of *Staphylococcus epidermidis* CRS. They found that leaking secondary to a defective attachment to the catheter hub was associated somehow with local microorganisms proliferation, and they postulated subsequent migration along the catheter tract. In our opinion they could not provide a satisfactory explanation, because the hub was not contemplated as the potential source of infection and cultures were not taken. We believe that in this situation the pathogenesis of CRS can be best explained by colonization of the inner surface of the catheter hub, intraluminal progression, tip infection, and, finally, sepsis. An analogous mechanism of sepsis has been recently desribed (20) in indwelling arterial lines for hemodynamic monitoring and arterial sampling; in one case the arterial catheter tip, stopcock, and the blood of the patient showed the same organism, without implicating skin infection. Brismar et al. have shown in their study (5) that sideports are a common route of bacterial contamination of infusion systems. In a consecutive series of experiments, we made several changes to reduce the risk of hub colonization (covering the hub with a sterile gauze embedded with

TABLE 1. CRS: results of cultures by quantitative (Q) and semiquantitative (SQ) methods

Source of infection	Case no.	Microorganism (blood and catheter)	Segment of catheter and method of culture[a]					TPN mixture	Skin	Distant sites of infection
			Intravascular (tip)		Subcutaneous		Hub			
			SQ	Q	SQ	Q	Q			
HUB	1	*Staphylococcus epidermidis*	>15 (+++)	$>10^3$	>15 (++)	$>10^3$	$>10^3$	–	–	–
	2	*Staphylococcus epidermidis*	>15 (+++)	$>10^3$	>15 (+)	$>10^3$	$>10^3$	–	*Staphylocccus simulans* (±)	–
	3	*Staphylococcus epidermidis*	>15 (+++)	$>10^3$	>15 (++)	$>10^3$	$>10^3$	–	*Staphylococcus haemolyticus* (±)	–
	4	*Staphylococcus epidermidis*	>15 (+)	$>10^3$	–	–	$>10^3$	–	–	–
	5	*Staphylococcus saprophyticus*	7 (±)	$>10^3$	2 (±)	320	$>10^3$	–	–	–
	6	*Staphylococcus epidermidis*	>15 (+++)	$>10^3$	>15 (++)	$>10^3$	$>10^3$	–	–	–
	7	*Staphylococcus haemolyticus*	>15 (+++)	$>10^3$	>15 (++)	240	$>10^3$	–	–	–
	8	*Staphylococcus epidermidis*	>15 (++)	$>10^3$	5 (±)	–	$>10^3$	–	–	–
	9	*Staphylococcus epidermidis*	>15 (+++)	$>10^3$	3 (±)	$>10^3$	$>10^3$	–	–	–
	10	*Staphylococcus epidermidis*	>15 (+++)	$>10^3$	>15 (++)	$>10^3$	$>10^3$	–	–	–
	11	*Staphylococcus epidermidis*	>15 (+++)	$>10^3$	>15 (++)	$>10^3$	$>10^3$	–	–	–
	12	*Staphylococcus epidermidis*	–	$>10^3$	–	$>10^3$	$>10^3$	–	–	–
	13	*Proteus mirabilis*	>15 (+++)	$>10^3$	>15 (+)	$>10^3$	$>10^3$	–	*Staphylococcus epidermidis* (+++)	Tracheostomy
	14	*Candida tropicalis*	>15 (+)	$>10^3$	–	$>10^3$	$>10^3$	–	–	–
TNP mixture	15	*Enterobacter cloacae*	>15 (+++)	$>10^3$	>15 (++)	$>10^3$	$>10^3$	*Enterobacter cloacae*	–	–
	16	*Enterobacter cloacae*	>15 (+++)	$>10^3$	–	$>10^3$	$>10^3$	*Enterobacter cloacae*	–	–
Hematogenous seeding	17	*Yersinia enterocolítica*	>15 (+++)	$>10^3$	>15 (+++)	$>10^3$	–	–	–	Perianal fistulae
	18	*Streptococcus faecalis*	>15 (+++)	$>10^3$	>15 (+++)	$>10^3$	–	–	–	Urine
Skin	19	*Staphylococcus aureus*	>15 (+++)	$>10^3$	>15 (+++)	$>10^3$	–	–	*Staphylococcus aureus* (+++)	–
	20	*Staphylococcus aureus*	>15 (+++)	–	>15 (+++)	–	–	–	*Staphylococcus aureus* (+++)	–

[a] –, Negative; ±, <15 CFU; +, 15 to 50 CFU; ++, 50 to 100 CFU; +++, >100 CFU.

povidone iodine ointment and changing the giving set twice a week, instead of daily) and the sepsis rate decreased from 39.5% to 5.7% ($X^2 = 27.3$; $P < 0.001$) (A. Sitges-Serra, J. Liñares, J. L. Pérez, E. Jaurrieta, and L. Lorente, J. Parenteral Enteral Nutr., in press). Also, Hesselrik et al. (9) and Holm and Wretlind (10) have prevented catheter-related sepsis by daily heating of metallic hubs. Since the hub is the cause of most cases of CRS, efforts should be made to diagnose early colonization, and we are currently evaluating the value of routine swab cultures of catheter hubs as a potentially useful diagnostic tool of one of the commonest types of catheter colonization.

Our methodology, with simultaneous use of Q and SQ techniques, has allowed us to differentiate between internal and external colonization of each catheter segment and to clarify the route of infection, a point that could not be clearly demonstrated by previous qualitative methods. In the Q method of Cleri et al. (6), the intravascular catheter segment is immersed in TSB and flushed three times; in so doing, it is impossible to discriminate between intra- and extraluminal colonization. To obtain precise information from the inner catheter surface, we modified the method conveniently: first, the external catheter surface was cultured by SQ method, and then the catheter lumen was flushed with 2 ml of TSB without immersion. In our series the SQ method produced positive cultures in the two cases of skin infection, reflecting counts of microorganisms present within the catheter wound, but it also produced positive cultures in 17 cases of catheter sepsis of other origins. These findings suggest that microorganisms colonize the fibrin sleeve formed inside and around most vascular catheters (11) if enough time elapses from the outset. We and others (4, 23) believe that routine culture of the subcutaneous segment is unnecessary and does not prove useful in diagnosing CRS, whereas the tip is the most important site of bacterial growth associated with sepsis. Likewise, catheter cultures in broth should be discarded because even a minute bacterial inocula from skin flora can give a false-positive broth culture.

In conclusion, the present study shows that hub colonization is a primary source of CRS. Other pathways are operative, but are rare today when TPN mixture preparation and catheter care standards are high. The prospective and systematic study of catheter segments by the SQ and Q techniques have allowed us to identify another as yet undescribed pathogenic mechanism of CRS caused by coagulase-negative staphylococci in patients on TPN.

LITERATURE CITED

1. **Bauer, A. W., W. M. Kirby, J. C. Sherris, and M. Turck.** 1966. Antibiotic susceptibility testing by a standardized single disk method. Am. J. Clin. Pathol. **45**:493–496.
2. **Bjornson, H. S., R. Colley, R. H. Bower, V. P. Duty, J. T. Schwartz-Fulton, and J. E. Fischer.** 1982. Association between microorganisms growth at the catheter insertion site and colonization of the catheter in patients receiving total parenteral nutrition. Surgery **92**:720–727.
3. **Blackett, R. L., A. Bakran, J. A. Bradley, A. Halsall, G. L. Hill, and M. J. Mahon.** 1978. A prospective study of subclavian vein catheters used exclusively for the purpose of intravenous feeding. Br. J. Surg. **65**:393–395.
4. **Bozzetti, F., G. Terno, E. Camerini, F. Baticci, D. Scarpa, and A. Pupa.** 1982. Pathogenesis and predictability of central venous catheter sepsis. Surgery **91**:383–389.
5. **Brisman, B., A. S. Malmborg, B. Nyström, and Ä. Strandberg.** 1984. Bacterial contamination of intravenous cannula injection ports and stopcocks. Clin. Nutr. **3**:23–26.
6. **Cleri, D. J., M. L. Corrado, and S. J. Seligman.** 1980. Quantitative culture of intravenous catheters and other intravascular inserts. J. Infect. Dis. **141**:781–786.
7. **Deitel, M., S. Krajden, C. F. Saldanha, W. D. Gregory, M. Fuksa, and E. Cantwell.** 1983. An outbreak of *Staphylococcus epidermidis* septicemia. JPEN **7**:569–572.
8. **Garden, O. J., and A. J. W. Sim.** 1983. A comparison of tunneled and nontunneled subclavian vein catheters: a prospective study of complications during parenteral feeding. Clin. Nutr. **2**:51–54.
9. **Hesselrik, F., B. Schildt, and B. Nilehn.** 1982. Long term parenteral therapy by percutaneous tunneled silicone central venous catheter. A follow-up of 300 catheters. Clin. Nutr. **1**:117–124.
10. **Holm, I., and A. Wretlind.** 1975. Prophylaxis against the infection and septicemia in parenteral nutrition via central intravenous catheter. Acta Chir. Scand. **141**:173–181.
11. **Hoshal, V. L., R. G. Ause, and P. A. Hoskins.** 1971. Fibrin sleeve formation on indwelling subclavian central venous catheters. Arch. Surg. **102**:353–358.
12. **Jones, R. N., C. Thornsberry, A. L. Barry, and T. L. Gavan.** 1981. Evaluation of the Sceptor microdilution antibiotic susceptibility testing system: a collaborative investigation. J. Clin. Microbiol. **13**:184–194.
13. **Keoane, P. P., B. J. M. Jones, H. Attrill, A. Cribb, J. Northover, P. Frost, and D. B. A. Silk.** 1983. Effect of catheter tunneling and a nutrition nurse on catheter sepsis during parenteral nutrition. A controlled trail. Lancet **ii**:1388–1390.
14. **Kloos, W. E., and P. B. Smith.** 1980. Staphylococci, p. 83–87. *In* E. H. Lennette, A. Ballows, W. J. Hausler, and J. P. Truant (ed.), Manual of Clinical Microbiology, 3rd ed. American Society for Microbiology, Washington, D.C.
15. **Maki, D. G.** 1977. Sepsis arising from extrinsic contamination of the infusion and measures for control, p. 99–141. *In* I. Phillips (ed.), Microbiologic hazards of intravenous therapy. MTP Press, Ltd. Lancaster, England.
16. **Maki, D. G.** 1982. Infections associated with intravascular lines, p. 309–363. *In* J. S. Remington and M. N. Swartz (ed.). Current clinical topics in infectious diseases—3. McGraw-Hill Book Co., New York.
17. **Maki, D. G., and C. J. Alvarado.** 1982. The role of clinical microbiology laboratory in diagnosis of infusion related sepsis. Clin. Microbiol. Newsletter **4**:89–94.
18. **Maki, D. G., C. E. Weise, and H. W. Sarafin.** 1977. A semiquantitative culture method for identifying intravenous-catheter related infection. N. Engl. J. Med. **296**:1305–1309.
19. **Ryan, J. A., R. M. Abel, W. M. Abbott, C. C. Hopkins, T. M. Chesney, R. Colley, K. Phillips, and J. E. Fischer.** 1974. Catheter complication in total parenteral nutrition. A prospective study of 200 consecutive patients. N. Engl. J. Med. **290**:757–761.
20. **Shinozaki, T., R. S. Deane, J. E. Mazuzan, A. J. Hamel, and D. Hazelton.** 1983. Bacterial contamination of arterial lines. J. Am. Med. Assoc. **249**:223–225.
21. **Sitges-Serra, A., E. Jaurrieta, J. Liñares, J. L. Pérez, and J. Garau.** 1983. Bacteria in total parenteral nutrition catheters: where do they come from? Lancet **ii**:531.
22. **Sitges-Serra, A., and J. Liñares.** 1984. Tunnels do not protect against venous catheter-related sepsis. Lancet **ii**:459–460.
23. **Sitges-Serra, A., P. Puig, E. Jaurrieta, J. Garau, A. Alastrue, and A. Sitges-Creus.** 1980. Catheter sepsis due to *Staphylococcus epidermidis* during parenteral nutrition. Surg. Gynecol. Obstet. **151**:481–483.
24. **Sitges-Serra, A., P. Puig, J. Liñares, J. L. Pérez, N. Farrero, E. Jaurrieta, and J. Garau.** 1984. Hub colonization as the initial step in an outbreak of catheter-related sepsis due to coagulase-negative staphylococci during parenteral nutrition. J. Parenteral Enteral Nutr. **8**:668–672.