

## Rationale for Selective Use of Anaerobic Blood Cultures

ARTHUR J. MORRIS,\* MICHAEL L. WILSON, STANLEY MIRRETT, AND L. BARTH RELLER  
*Clinical Microbiology Laboratory, Duke University Medical Center, Durham, North Carolina 27710*

Received 5 March 1993/Accepted 24 May 1993

Because of the declining frequency of anaerobic bacteremia, routinely using half the collected blood volume for anaerobic culture has been challenged. There is no data indicating whether more clinically relevant isolates would be recovered if all or most of the given blood sample were cultured aerobically. In this two-part study, we reviewed cases of anaerobic bacteremia to determine what proportion occurred in situations when anaerobes would be expected and then estimated the yield of different culture approaches by reanalyzing the data from a large prospective clinical blood culture study. The records of 61 patients who had an anaerobic isolate (excluding *Propionibacterium* species) recovered only from an anaerobic bottle were examined to define clinical settings in which such isolates occur. Fifty-six (92%) patients had clinically important isolates, and the source of infection was obvious at the time of culture in 47 of the 56 (84%). Of 56 patients, 36 (64%) had abdominal signs and symptoms, including 12 with recent abdominal surgery. Of nine patients without an obvious source of infection, six were on high-dose steroids. Relative yields were compared for (i) one aerobic bottle and one anaerobic bottle (5 ml to each) for all blood cultures, (ii) two aerobic bottles (5 ml to each), or (iii) two aerobic bottles plus an extra anaerobic bottle (only for clinically suspected anaerobic sepsis) (5 ml to each). The third approach had the highest yield (475 isolates), because the routine use of two aerobic bottles recovered more *Candida* spp., members of the family *Enterobacteriaceae*, and nonfermenters than did the first approach (448 isolates) ( $P < 0.02$ ), and clinically directed culturing for anaerobes would recover anaerobes missed with the second approach (458 isolates). Our data suggest that the use of two aerobic bottles with selective culturing for anaerobes could increase the number of clinically relevant isolates by at least 6% compared with the current practice of inoculating an aerobic bottle and an anaerobic bottle with equal volumes of blood.

Over the past 15 years there has been a decline in the proportion of positive blood cultures that yield anaerobic bacteria, whereas the proportion with *Candida* spp. has increased (9, 10, 20, 23, 28, 35). Consequently, the routine inoculation of an anaerobic bottle has been called into question (23, 28). Data have not been presented, however, to estimate how many more clinically important isolates might be recovered if the entire blood sample were cultured aerobically, rather than routinely using half the sample for anaerobic culture.

We have retrospectively reviewed the charts of patients with anaerobic isolates found only in the anaerobic bottle at our medical center to define the clinical settings in which such bacteremia occurs in our hospital. By using these data and reanalyzing the results from a prospective multicenter blood culture study (34), we present an estimate of the likely increase in clinically relevant isolates if blood were routinely inoculated into two aerobic bottles and if an anaerobic bottle was used only for patients at recognized risk for anaerobic bacteremia.

### MATERIALS AND METHODS

Records in the Clinical Microbiology Laboratory at Duke University Medical Center, a 1,125-bed tertiary-care hospital, were reviewed for strict anaerobes recovered only from the anaerobic bottles of blood culture sets during August 1989 through February 1991. The charts of patients with anaerobic isolates were examined to (i) determine the clinical importance of such isolates and (ii) record the clinical situations in which these isolates occurred.

Results of a prospective multicenter clinical comparison of

nonradiometric BACTEC and BacT/Alert systems (34) were reanalyzed to calculate the relative yield from blood divided into (i) one aerobic and one anaerobic bottle (5 ml of blood inoculated into each), (ii) two aerobic bottles (5 ml of blood inoculated into each), (iii) two aerobic bottles and a 5-ml anaerobic bottle for all patients, or (iv) two aerobic bottles plus an extra 5-ml anaerobic bottle only for patients at risk clinically for anaerobic sepsis. This controlled trial compared 5,918 pairs of aerobic bottles and 5,992 pairs of anaerobic bottles (34). In this study, 20 ml of blood was collected at the bedside and 5 ml was inoculated immediately into each of the four blood culture bottles. Only adequately (4 to 6 ml) filled bottles were analyzed for yield. Only isolates deemed clinically relevant were included in the analysis; contaminants were ignored. The overall recoveries of microorganisms from the two aerobic and two anaerobic bottles were comparable (34). For the purposes of this study, the two systems were regarded as being equivalent, which enabled us to calculate the yield from various combinations (details above) of inoculated bottles. We arbitrarily chose the BACTEC anaerobic bottle for analysis of the yield from 5 ml of blood inoculated anaerobically. This system is equivalent to the BacT/Alert anaerobic system (34).

Two assumptions were made in estimating the yield for selective anaerobic blood culture on clinical grounds. First, the estimate of how many obligate anaerobes would be detected with the selective use of the anaerobic bottle was made by applying the proportion of patients at Duke University Medical Center with anaerobic bacteremia who had signs and symptoms at a site where anaerobes are expected (84% [see below]) to the yield from routinely using an anaerobic bottle in the prospective blood culture evaluation as described above. Second, credit was given only for recovering obligate anaerobes in the anaerobic bottle.

\* Corresponding author.

TABLE 1. Features of nine patients with anaerobic bacteremia who did not have an obvious site of anaerobic infection

Patient no.	Sex <sup>a</sup>	Age (yr)	Blood isolate(s)	Steroids <sup>b</sup>	Clinical symptoms <sup>c</sup>	Outcome
1	M	49	<i>C. tertium</i>	+	ALL and chemotherapy-induced neutropenia	Died
2	M	78	<i>Clostridium clostridioforme</i> , <i>Bacteroides ovatus</i>	+	CLL, fever, and hypotension	Died
3	M	79	<i>C. tertium</i> , <i>Bacteroides thetaiotaomicron</i>	+	ALL, fever, and chemotherapy-induced neutropenia	Died
4	M	87	<i>Clostridium ramosum</i>	+	CLL, fever, and chemotherapy-induced neutropenia	Died
5	M	54	<i>Clostridium innocuum</i>	+	Lymphoma and chemotherapy-induced neutropenia	Died
6	M	75	<i>B. thetaiotaomicron</i>	+	Spontaneous vertebral compression fracture	Died
7	M	58	<i>B. thetaiotaomicron</i> , <i>Peptostreptococcus micros</i>	-	Infected abdominal aortic graft	Lived
8	M	48	<i>C. tertium</i>	-	Gastric lymphoma, chemotherapy, and gastrointestinal bleeding	Died
9	F	35	<i>Fusobacterium</i> sp.	-	Symptoms of pyelonephritis, treated, and discharged. Returned no better 2 days later. Extensive PID at operation.	Lived

<sup>a</sup> M, male; F, female.

<sup>b</sup> High-dose prednisone or equivalent.

<sup>c</sup> ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; PID, pelvic inflammatory disease.

## RESULTS

Over the 19-month period, 62 patients had an anaerobic organism isolated only from an anaerobic blood culture bottle. One patient's chart could not be located for review. Five isolates (8%) were considered contaminants (three *Clostridium perfringens*, one unidentified gram-positive rod, and one *Anaerobiospirillum succiniciproducens*). Fifty-six (92%) patients had 66 clinically important isolates: 13 *Bacteroides fragilis*, 12 *B. fragilis* group, and 5 other *Bacteroides* species; 4 *Clostridium tertium*, 3 *Clostridium septicum*, 3 *Clostridium ramosum*, and 9 other *Clostridium* isolates; 7 peptostreptococci; 3 *Fusobacterium* species; 1 *Wolinella* species; 2 unidentified gram-negative rods; and 4 gram-positive bacilli.

Eight (14%) patients had mixed anaerobes. Twelve (21%) patients had clinically significant aerobic organisms recovered from the aerobic bottle of the same set containing the anaerobe isolate(s) (specifically, members of the family *Enterobacteriaceae*, 7 patients; *Staphylococcus aureus*, 2

patients; *Candida* sp., 1 patient; mixed oral flora, 1 patient; and *Enterococcus* sp., 1 patient).

Of 56 patients, 47 (84%) patients had signs and symptoms at a site where anaerobes could be expected. Thirty-six of the 56 patients (64%) had an abdominal infection source: 31 had abdominal signs and symptoms, of whom 12 had had recent abdominal surgery, and 5 with abdominal signs and symptoms had chemotherapy-induced neutropenia. Five of the 56 patients (9%) had end-stage liver failure with repeated gastrointestinal bleeding. Two women had pelvic infections. One patient had sacral decubitus. One patient had a fetid foot. One patient with neutropenia had extensive esophageal ulceration. One patient had a putrid lung abscess and empyema. Nine of the 56 (16%) patients did not have an obvious site of anaerobic infection (Table 1). Six of these nine patients were on high-dose steroids. Ten patients were neutropenic, and *Clostridium* spp. were recovered in nine. The four neutropenic patients who did not have signs and symptoms suggesting a site where anaerobes could be ex-

TABLE 2. Actual and estimated yields of significant isolates recovered from blood by four culture methods<sup>a</sup>

Bacteria	No. of isolates recovered from bottles inoculated with the indicated volume:			
	10 ml		15 ml	
	5-ml O <sub>2</sub> and 5-ml ANO <sub>2</sub>	5-ml O <sub>2</sub> and 5-ml O <sub>2</sub>	2 5-ml O <sub>2</sub> and routine 5-ml ANO <sub>2</sub>	2 5-ml O <sub>2</sub> and selective 5-ml ANO <sub>2</sub>
Staphylococci	180	181	193	181
Streptococci	63	58	69	58
<i>Enterobacteriaceae</i>	114	129	137	129
Nonfermenters	23	29	29	29
<i>Candida</i> spp.	41	53	54	53
ANO <sub>2</sub> gram-positive bacilli	15	8	17	15 <sup>b</sup>
ANO <sub>2</sub> gram-negative bacilli	12	0	12	10 <sup>b</sup>
Total	448	458	511	475

<sup>a</sup> O<sub>2</sub>, aerobic; ANO<sub>2</sub>, anaerobic.

<sup>b</sup> Estimated from the review of anaerobic bacteremia that 84% of anaerobic bacteremias occur in patients at readily recognized risk.

pected were on high-dose steroids (Table 1). Thirty (54%) patients died.

The actual and estimated yields of clinically relevant isolates recovered for different culture methods are shown in Table 2. Inoculation of one aerobic bottle and one anaerobic bottle yielded 448 clinically relevant isolates. Inoculation of two aerobic bottles yielded more isolates of members of the family *Enterobacteriaceae* (15 isolates), *Candida* spp. (12 isolates), nonfermenters (6 isolates), and staphylococcal (1 isolate) (34 more isolates) than the standard aerobic and anaerobic bottle approach ( $P < 0.02$ ) at the expense of missing 7 of 15 anaerobic gram-positive bacilli, all 12 anaerobic gram-negative bacilli, and 5 streptococci (24 fewer isolates). The routine use of an anaerobic bottle with two aerobic bottles recovered more staphylococci, streptococci, and *Enterobacteriaceae* (31 more isolates) in addition to the 19 anaerobes missed by the two aerobic bottles (Table 2). We estimated that the selective use of an anaerobic bottle in addition to two aerobic bottles could detect 84% of the obligate anaerobes detected by the routine use of an anaerobic bottle (based on the clinical review above) as well as the increased yield of *Enterobacteriaceae*, nonfermenters, and *Candida* spp. in the two aerobic bottles (Table 2). This approach yielded 475 isolates compared with 448 isolates obtained with one aerobic and one anaerobic bottle, a 6% increase that could be attributed to culturing the entire blood sample aerobically with only selective use of anaerobic bottles. We did not give the selective use of the anaerobic bottle credit for recovering any of the 31 staphylococci, streptococci, and *Enterobacteriaceae* recovered by its routine use (Table 2), because it is unknown how many of those isolates were obtained from clinical settings where anaerobes could be expected, that is, when an anaerobic bottle would have been used selectively.

## DISCUSSION

The proportion of positive blood cultures yielding anaerobes has decreased from about 10 to 15% in the 1970s to less than 5% in more recent blood culture series (9, 20, 23, 28). All the reasons for this decrease are unknown, but many have been proposed: earlier recognition and treatment of anaerobic infection, empiric antimicrobial therapy with agents with anaerobic activity, changing patient populations, and preoperative use of agents before bowel surgery (9, 20, 23, 28); the last has data to support it (1). This decline has led some to question the routine use of half the blood volume for anaerobic culture and to suggest that anaerobic cultures be reserved for those clinical settings where anaerobes are known to be important (23, 28).

In our hospital, most (84%) patients with anaerobic bacteremia detected only in an anaerobic blood culture bottle had signs and symptoms indicating a site where anaerobes would be expected. This proportion is in close agreement (87 and 92%, respectively) with two recent reports (3, 20). The majority of our isolates (64%) originated from the abdomen. Other reports have implicated the gastrointestinal tract as the source for 42 to 65% of anaerobic blood isolates (2, 3, 5, 14, 18, 20). The other sites encountered were similar to those described previously (3, 5, 14, 18).

Nine patients did not have signs or symptoms referable to a site where anaerobes could be expected. Six of these patients were on high-dose steroids, which may have masked patient symptoms. Although others have mentioned the association between steroids and anaerobic bacteremia (2, 14), no specific information is provided about the pres-

ence or absence of symptoms. In Lombardi and Engleberg's blood culture series, two of the five patients with an unknown source were febrile neutropenic patients but there was no information regarding steroid therapy (20). Almost all (9 of 10) of the neutropenic patients had *Clostridium* bacteremia, and *C. tertium* and *C. septicum* predominated. This association has been well-described (19, 29-31).

If 10 ml of blood is obtained for culture, more clinically important isolates would be recovered if the entire sample were cultured aerobically than are recovered by the current practice of culturing half anaerobically. This is because more members of the family *Enterobacteriaceae*, nonfermenters, and yeasts would be recovered from the blood which would otherwise have been incubated anaerobically. The current practice of equal division of blood for aerobic and anaerobic culture reduces the yield of significant aerobic isolates when the prevalence of anaerobic bacteremia is low.

If one has to choose between detecting more yeasts, members of the family *Enterobacteriaceae*, and nonfermenters and detecting more anaerobes, it appears to us that the former would have greater clinical utility. Antimicrobial susceptibilities of anaerobes are more reliably predictable than those of *Enterobacteriaceae* or nonfermenters; several antimicrobial agents have almost universal activity for anaerobes (6, 7, 11, 12, 14, 15, 17, 24, 33). Although it is true that some researchers have observed changes in the susceptibilities of anaerobic isolates (8, 13, 26), susceptibility testing is seldom required for an individual patient, even though certain exceptions exist (15, 25). Not all yeasts are susceptible to amphotericin B or fluconazole and the identification of a yeast isolate can be helpful in suggesting its likely susceptibility (4, 16, 21, 22, 27, 32, 36). Neither identification nor susceptibility testing is possible if the isolate is by chance distributed in the half of the blood sample cultured in the inhospitable milieu of an anaerobic bottle.

The hope that more clinically relevant organisms would be recovered with the two aerobic bottle approach may not be realized if enough facultative anaerobic bacteria (e.g., streptococci, staphylococci, and members of the family *Enterobacteriaceae*) fail to grow because they were not inoculated into an anaerobic bottle. As Murray et al. (23) have indicated, the major benefit of the unvented bottle may be the recovery of facultative anaerobes that preferentially grow in anaerobic bottles. We observed some evidence for this (Table 2). The total number of anaerobic isolates was 27, yet the routine use of an anaerobic bottle in addition to two aerobic bottles recovered 31 facultative anaerobic bacteria (12 staphylococci, 11 streptococci, and 8 *Enterobacteriaceae* [Table 2]). We had no way of telling how many of these 31 isolates were obtained in settings where anaerobes could be expected, but it is reasonable to assume that some of the streptococcal and *Enterobacteriaceae* isolates would have been detected. Therefore, selective use of anaerobic cultures may recover clinically relevant facultative anaerobes in addition to most anaerobes.

Establishing and monitoring a policy for selective use of anaerobic blood cultures requires that logistical issues be addressed. Possible approaches include prepackaged collection kits with two aerobic bottles with a note of when anaerobic culture is indicated; specially trained blood culture teams; and arbitrarily restricting anaerobic bottles to certain wards, for example, colorectal and gynecologic surgical services.

Anaerobic cultures should be reserved for patients for whom there is clinical evidence of infection at a site where

anaerobes are likely. Neutropenic patients on steroids represent a group for whom anaerobic cultures also should be considered even in the absence of symptoms referable to the abdomen (Table 1). By our analysis, the routine aerobic culturing of the entire volume of 10 to 20 ml of blood from an independent venipuncture from an adult and the selective use of anaerobic blood cultures would likely increase the overall yield of clinically important isolates by about 6%. This approach is already common in pediatric patients where the prudent volume of available blood for culture is much less. Proof of our prediction requires an appropriately designed prospective clinical trial.

## REFERENCES

- Bartlett, J. G., R. E. Condon, L. S. Gorbach, J. S. Clarke, R. L. Nichols, and S. Ochi. 1978. Veterans Administration cooperative study on bowel preparation for elective colorectal operations: impact of oral antibiotic regimen on colonic flora, wound irrigation cultures, and bacteriology of septic complications. *Ann. Surg.* **188**:249-254.
- Bodner, S. J., M. G. Koenig, and J. S. Goodman. 1970. Bacteremic bacteroides infections. *Ann. Intern. Med.* **73**:537-544.
- Brook, I. 1989. Anaerobic bacterial bacteremia: 12-year experience in two military hospitals. *J. Infect. Dis.* **160**:1071-1075.
- Case, C. P., A. P. MacGowan, N. M. Brown, D. S. Reeves, P. Whitehead, and D. Felmingham. 1991. Prophylactic oral fluconazole and candida fungaemia. *Lancet* **337**:790.
- Chow, A. W., and L. B. Guze. 1974. *Bacteroidaceae* bacteremia: clinical experience with 112 patients. *Medicine* **53**:93-126.
- Cuchural, G. J., Jr., F. P. Tally, N. V. Jacobus, T. Cleary, S. M. Finegold, G. Hill, P. Iannini, J. P. O'Keefe, and C. Pierson. 1990. Comparative activities of newer  $\beta$ -lactam agents against members of the *Bacteroides fragilis* group. *Antimicrob. Agents Chemother.* **34**:479-480.
- Cuchural, G. J., Jr., F. P. Tally, N. V. Jacobus, S. L. Gorbach, K. Aldridge, T. Cleary, S. M. Finegold, G. Hill, P. Iannini, J. P. O'Keefe, C. Pierson, C. Derrick, T. Russo, and D. Hecht. 1988. Susceptibility of the *Bacteroides fragilis* group in the United States: analysis by site of isolation. *Antimicrob. Agents Chemother.* **32**:717-722.
- De Almeida, A. E., and M. De Uzeda. 1987. Susceptibility to five antimicrobial agents of strains of the *Bacteroides fragilis* group isolated in Brazil. *Antimicrob. Agents Chemother.* **31**:617-618.
- Dorsher, C. W., J. E. Rosenblatt, W. R. Wilson, and D. M. Ilstrup. 1991. Anaerobic bacteremia: decreasing rate over a 15-year period. *Rev. Infect. Dis.* **13**:633-636.
- Dorsher, C. W., W. R. Wilson, and J. E. Rosenblatt. 1989. Anaerobic bacteremia and cardiovascular infections, p. 289-310. In S. M. Finegold and W. L. George (ed.), *Anaerobic infections in humans*. Academic Press, Inc., San Diego, Calif.
- Downes, J., and J. H. Andrew. 1988. Susceptibility of 114 isolates of the *Bacteroides fragilis* group to imipenem and eight other antimicrobial agents. *Pathology* **20**:260-263.
- Edson, R. S., J. E. Rosenblatt, D. T. Lee, and E. A. McVey III. 1982. Recent experience with antimicrobial susceptibility of anaerobic bacteria. *Mayo Clin. Proc.* **57**:737-741.
- Elhag, K. M., A. K. Mustafa, and A. A. Pazhoor. 1989. The changing pattern of antibiotic susceptibilities of *Bacteroides fragilis* in Kuwait. *J. Antimicrob. Chemother.* **24**:699-707.
- Felner, J. M., and V. R. Dowell, Jr. 1971. "Bacteroides" bacteremia. *Am. J. Med.* **50**:787-796.
- Finegold, S. M. 1990. Anaerobes: problems and controversies in bacteriology, infections, and susceptibility testing. *Rev. Infect. Dis.* **12**(Suppl.):S223-S230.
- Hadfield, T. L., M. B. Smith, R. E. Winn, M. G. Rinaldi, and C. Guerra. 1987. Mycoses caused by *Candida lusitanae*. *Rev. Infect. Dis.* **9**:1006-1012.
- Henderson, G., J. Garner, and A. Morris. 1992. Antimicrobial susceptibility of anaerobic bacteria in Auckland 1987-90. *N.Z. Med. J.* **105**:10-12.
- Ingram, C. W., and J. N. Cooper. 1989. Clostridial bloodstream infections. *South. Med. J.* **82**:29-31.
- Katlic, M. R., W. M. Derkac, and W. S. Coleman. 1981. *Clostridium septicum* infection and malignancy. *Ann. Surg.* **193**:361-364.
- Lombardi, D. P., and N. C. Engleberg. 1992. Anaerobic bacteremia: incidence, patient characteristics, and clinical significance. *Am. J. Med.* **92**:53-60.
- Merz, W. G. 1984. *Candida lusitanae*: frequency of recovery, colonization, infection, and amphotericin B resistance. *J. Clin. Microbiol.* **20**:1194-1195.
- Morace, G., S. Manzara, and G. Dettori. 1991. *In vitro* susceptibility of 119 yeast isolates to fluconazole, 5-fluorocytosine, amphotericin B and ketoconazole. *Chemotherapy (Basel)* **91**:23-31.
- Murray, P. R., P. Traynor, and D. Hopson. 1992. Critical assessment of blood culture techniques: analysis of recovery of obligate and facultative anaerobes, strict aerobic bacteria, and fungi in aerobic and anaerobic blood culture bottles. *J. Clin. Microbiol.* **30**:1462-1468.
- Musial, C. E., and J. E. Rosenblatt. 1989. Antimicrobial susceptibilities of anaerobic bacteria isolated at the Mayo Clinic during 1982 through 1987: comparison with results from 1977 through 1981. *Mayo Clin. Proc.* **64**:392-399.
- National Committee for Clinical Laboratory Standards. 1990. Methods for antimicrobial susceptibility testing of anaerobic bacteria, 2nd ed. Approved standard. NCCLS publication M11-A2. National Committee for Clinical Laboratory Standards, Villanova, Pa.
- Peláez, M. T., E. Cercenado, M. Rodríguez-Crèixems, and E. Bouza. 1991. Resistance of anaerobic bacteria to antimicrobial agents. *Rev. Infect. Dis.* **13**:183-184.
- Persons, D. A., M. Laughlin, D. Tanner, J. Perfect, J. P. Gockerman, and J. W. Hathorn. 1991. Fluconazole and *Candida krusei* fungemia. *N. Engl. J. Med.* **325**:1315.
- Sharp, S. E. 1991. Routine anaerobic blood cultures: still appropriate today? *Clin. Microbiol. Newsl.* **13**:179-181.
- Speirs, G., R. W. Warren, and A. Rampling. 1988. *Clostridium tertium* septicemia in patients with neutropenia. *J. Infect. Dis.* **158**:1336-1340.
- Thaler, M., V. Gill, and P. A. Pizzo. 1986. Emergence of *Clostridium tertium* as a pathogen in neutropenic patients. *Am. J. Med.* **81**:596-600.
- Valtonen, M., A. Sivonen, and E. Elonen. 1990. A cluster of seven cases of *Clostridium tertium* septicemia in neutropenic patients. *Eur. J. Clin. Microbiol. Infect. Dis.* **1**:40-42.
- Warnock, D. W., J. Burke, N. J. Cope, E. M. Johnson, N. A. Von Fraunhofer, and E. W. Williams. 1988. Fluconazole resistance in *Candida glabrata*. *Lancet* **ii**:1310.
- Wexler, H. M., B. Harris, W. T. Carter, and S. M. Finegold. 1986. Six-year retrospective survey of the resistance of *Bacteroides fragilis* group species to clindamycin and cefoxitin. *Diagn. Microbiol. Infect. Dis.* **4**:247-253.
- Wilson, M. L., M. P. Weinstein, L. G. Reimer, S. Mirrett, and L. B. Reller. 1992. Controlled comparison of the BacT/Alert and BACTEC 660/730 nonradiometric blood culture systems. *J. Clin. Microbiol.* **30**:323-329.
- Wilson, W. R., W. J. Martin, C. J. Wilkowske, and J. A. Washington II. 1972. Anaerobic bacteremia. *Mayo Clin. Proc.* **47**:639-646.
- Wingard, J. R., W. G. Merz, M. G. Rinaldi, T. R. Johnson, J. E. Karp, and R. Saral. 1991. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. *N. Engl. J. Med.* **325**:1274-1277.