MAJOR ARTICLE

# Revisiting the Source of Candidemia: Skin or Gut?

**Marcio Nucci[1] and Elias Anaissie[2]**

[1]University Hospital, Universidade Federal do Rio de Janeiro, Brazil; and [2]University of Arkansas for Medical Sciences, Little Rock

**The source of candidemia has been the subject of considerable debate, with some suggesting a origin in the gastrointestinal tract and others suggesting a skin origin. To evaluate the potential sources of candidemia, we performed a computerized search of the MEDLINE database for studies published from January 1966 through September 2000 and we identified relevant abstracts presented at national meetings. We reviewed the literature with special emphasis on studies that used appropriate definitions, evaluated both gut and skin as sources, and conducted molecular-relatedness studies. Among 203 candidemia studies published, we identified 21 that evaluated a specific source for candidemia and only 5 that performed molecular typing. Those studies and additional experimental, epidemiologic, and molecular-relatedness studies strongly suggested that the gut is an important source of candidemia, and studies that supported the skin as a source for this infection were surprisingly incomplete.**

The incidence of candidemia has increased substantially during the past 20 years [1], and *Candida* species now rank among the 4 pathogens most frequently isolated in blood cultures. The source of this infection has been the subject of considerable debate, with some suggesting the gastrointestinal tract (endogenous acquisition) [2] and others favoring the skin (exogenous acquisition) as a source [3, 4], the latter being implicated in the pathogenesis of catheter-related candidemia. Identification of the source of candidemia is important because of the implications for preventive strategies. Other sources of candidemia have also been hypothesized, including the genitourinary tract [5] and contaminated iv solutions [6]. In this article, we review studies that evaluated potential sources of candidemia with special emphasis on studies that used appropriate definitions, evaluated both gut and skin sources, and performed molecular-relatedness studies.

## METHODS

***Data source.*** We performed a computerized search of the MEDLINE database for studies published from January 1966 through November 2000 in any language. The keywords used were "candidemia," "*Candida*," "gut," "gastrointestinal tract," "skin," "molecular typing," "source," "origin," and "animal model." All abstracts published from 1987 through 2000 at the yearly meetings of the American Society for Microbiology, the Infectious Diseases Society of America, and the Society of Healthcare Epidemiology of America were also reviewed.

***Study selection.*** We focused on the papers that fulfilled the following criteria: (1) evaluation of the source of candidemia by investigation of prior colonization of the skin and/or the gastrointestinal tract and (2) use of molecular methods to support relatedness between colonizing and infecting strains. We required molecular-relatedness studies because of the

Received 5 March 2001; revised 30 May 2001; electronically published 8 November 2001.

Reprints or correspondence: Dr. Elias J. Anaissie, Clinical Affairs, Myeloma and Transplantation Research Center, University of Arkansas for Medical Sciences, 4301 West Markham, Slot 776, Little Rock, AR 72205 (anaissieeliasj@exchange.uams.edu).

**Clinical Infectious Diseases 2001;33:1959–67**



1058-4838/2001/3312-0001$03.00

genotypic diversity of *Candida* species [7]. Therefore, finding the same species at a colonizing site does not necessarily imply that the same organism is responsible for the bloodstream infection. We also evaluated the density and sequence of candida colonization and analyzed all of our findings according to patient population to find out whether the pathogenesis of candidemia differed among various patient populations.

***Data extraction.*** We reviewed methodology, definition of candidemia, source of candidemia, patient characteristics, and the results of surveillance cultures and molecular-relatedness studies.

## RESULTS

### Limitations of the Current Literature

We identified 203 candidemia studies (figure 1). Of those studies, only 21 had investigated specific sources of candidemia: 4 evaluated the skin [3, 4, 8, 9], 11 evaluated the gut [10–20], and 6 evaluated both sources [21–26]. Among these 21 studies, only 5 performed DNA typing: 4 studies that evaluated the gut [17–20] and 1 evaluated both the skin and gut [26].

### Findings: The Skin Hypothesis

***Experimental evidence.*** Theoretically, *Candida* species could enter the bloodstream from the skin via 2 routes: invasion from a skin lesion (e.g., burn wounds) or contamination of a vascular catheter from colonized skin (table 1). Therefore, an experimental model obtained by inoculating *Candida* organisms into a wound or the skin, followed by the insertion of a venous catheter at the inoculated site, should lead to hematogenous candidiasis. We could not identify such a model, which indicates that no experimental data support skin as the source of candidemia.

***Clinical evidence from epidemiological studies.*** Among the 4 studies that investigated only skin colonization, 2 were conducted using patients with burns. In 1 study, 50% of patients with candidemia had positive burn wound cultures [4]. However, no correlation between burn wound cultures and candidemia was made. In the other study, positive burn wound cultures were not predictors of candidemia, according to multivariate analysis [7].

Another study [9] performed skin surveillance cultures (umbilicus and groin) on 57 low–birth-weight infants admitted to

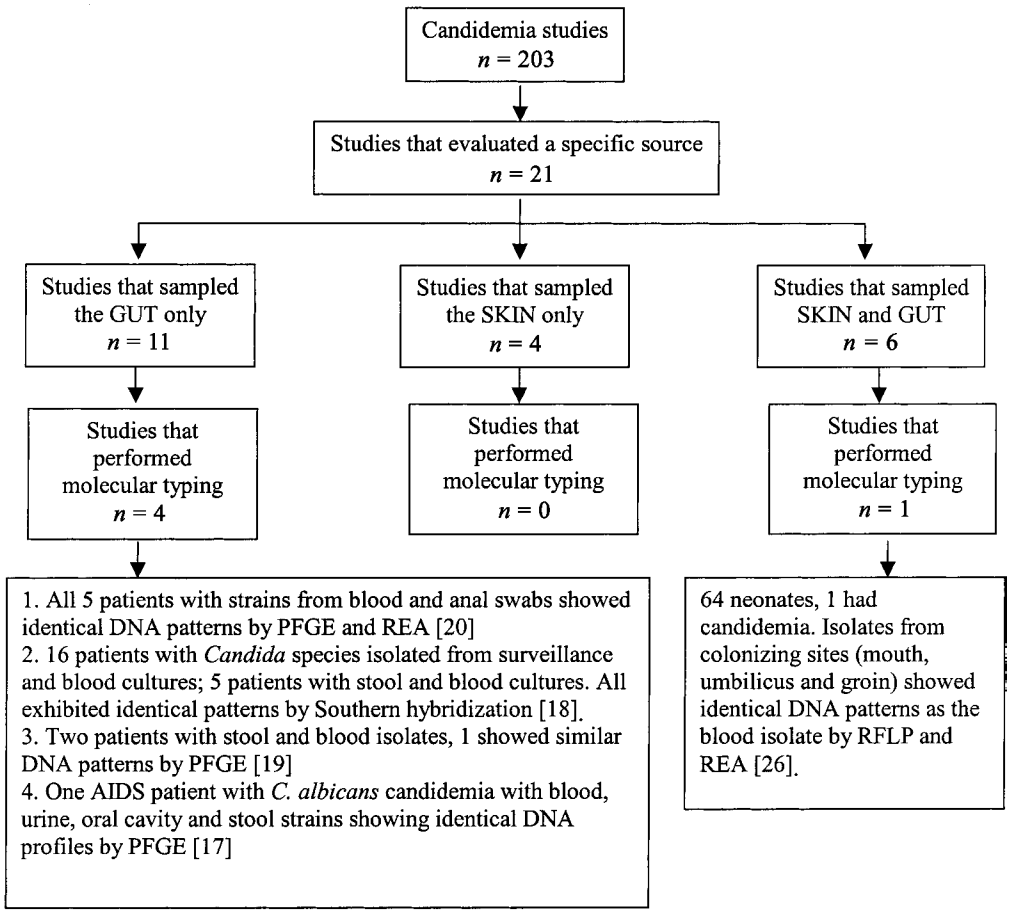


**Figure 1.** Selection of studies that evaluated the sources of candidemia. PFGE, pulsed-field gel electrophoresis; REA, restriction enzyme analysis; RFLP, restriction-fragment length polymorphism.

a neonatal unit. All 3 patients with candidemia had the same *Candida* species recovered from skin cultures.

In the fourth study [3], 53 patients who received parenteral nutrition were prospectively evaluated. At the time of catheter removal, cultures of skin samples obtained from the site of catheter insertion and of the intravascular (first 3 cm from the tip of the catheter) and the subcutaneous (1 cm distal to the site of dermal entry) segments of the catheter were performed. Six patients had candidemia, and in 2 patients, the same species was isolated from the blood, skin, and subcutaneous and intravascular segments of the catheter.

Two other studies evaluated skin and other sites as potential sources for candidemia. Sheridan et al. [21] retrospectively reviewed *Candida* colonization and infection in 962 children with burns by reviewing surveillance cultures of samples of the respiratory tract, wound, stool, and urine. All 17 patients with candidemia had the same species isolated from the wound samples, whereas only 35% of stool cultures yielded the same *Candida* species that was recovered from blood samples.

Huang et al. [23] prospectively evaluated 116 low–birth-weight infants with weekly cultures from specimens of oropharynx, rectum, skin (groin and axilla), urine, and endotracheal aspirates. Three patients developed candidemia, and 1 of these patients had prior colonization at 4 sites by the same species. However, the sites of positive cultures were not mentioned.

***Clinical evidence from molecular-relatedness studies.*** One report evaluated skin (and gut) colonization and performed molecular-relatedness studies with restriction enzyme analysis and restriction-fragment length polymorphism [26]. In this study, 64 neonates had weekly cultures of specimens of the oropharynx, umbilicus, groin, and iv site(s), starting in the first 24 h after birth. One of these neonates developed candidemia, and DNA typing showed an identical pattern of the strains isolated from blood, mouth, groin, and umbilicus samples. However, it is practically impossible to identify the primary source of infection in this single case, because, as shown by El-Mohandes et al. [25], the groin may have became secondarily colonized by strains that originated in the gastrointestinal tract, particularly given that the gut mucosa (mouth) harbored the same organism and that the sequence of colonization and infection in this patient was not evaluated.

***Density and sequence of colonization and infection.*** No studies have been published that support the skin hypothesis on the basis of density and sequence of candidal colonization.

### Findings: The Gut Hypothesis

***Experimental evidence: laboratory.*** A large number of experimental animal models of gastrointestinal colonization and disseminated infection have been published elsewhere [27]. In these models, candidal gut colonization is established through feeding the animals with a diet that contained *Candida* species. Immunosuppression of these colonized animals usually leads to disseminated candidiasis [28–34].

***Experimental evidence: clinical.*** A healthy human subject volunteered to receive an oral suspension of $\sim 10^{12}$ cells of *Candida albicans* and developed hematogenous candidiasis [35].

***Clinical evidence from epidemiological studies.*** El-Mohandes et al. [25] performed cultures of stool, gastric aspirate, and skin samples obtained from 82 neonates admitted to an intensive care unit. *Candida parapsilosis* was recovered in 75% of stool cultures and 80% of cultures of gastric aspirates. By contrast, only 50% of positive skin cultures yielded *C. parapsilosis.* Furthermore, positive stool cultures always preceded positive skin cultures, and the baseline stool cultures of all 4 patients with candidemia yielded *C. parapsilosis,* whereas baseline skin cultures were negative in these same patients.

In a prospective study, Bow et al. [10] showed that colonization by *Candida* species of sites other than the skin (e.g., nose, oropharynx, anus, and urine) was a risk factor for hematogenous candidiasis. Similar findings were reported in 2 studies by Martino et al. [12, 13]. Chryssanthou et al. [11] reported that 3 patients with candidemia (out of 277 patients with neutropenia) had the same *Candida* species isolated from stool and blood cultures.

MacFie et al. [14] prospectively studied 279 patients who underwent laparotomy and obtained cultures of gastric aspirates. *Candida* species were the organisms most frequently recovered from gastric aspirates (54%), and the same *Candida* species was recovered from blood and gastric aspirate in 1 patient with candidemia.

Pierro et al. [15] prospectively evaluated 94 infants who received parenteral nutrition with twice-weekly oral and anal swabs. Only 1 patient developed candidemia, and the same species *(C. albicans)* was isolated from the anal swab surveillance cultures and blood samples.

Pittet et al. [16] studied 650 critically ill surgical and neonatal patients with sequential cultures of samples of the oropharynx, trachea, and stomach. Among 29 patients with significant colonization (positive cultures in $\geqslant 3$ samples obtained from the same or different body sites on $\geqslant 2$ consecutive screening days), density of colonization was a good predictor of subsequent candidemia by multivariate analysis. The association between density of colonization and invasive candidiasis was also demonstrated in another study of surgical patients [36].

Two retrospective studies evaluated patients with cancer who had candidemia in which the researchers obtained samples of the skin and gut. In one study [22], gut (but not skin) colonization was a risk factor for candidemia by univariate analysis, whereas colonization at any site (skin, urine, oropharynx, or feces) was a risk factor for candidemia by multivariate analysis. The other study [24] also identified colonization at any site

**Table 1. Studies that evaluated the source of candidemia.**

| Source, author, year, and reference | Patients | Study design | Definitions of candidemia, source of blood collection | Sites of colonization sampled | Results and comments |
|---|---|---|---|---|---|
| Skin | | | | | |
| Schattuck 1996 [9] | 57 low–birth-weight neonates, 3 with candidemia | Prospective cohort | Definition not mentioned; blood was drawn from an iv catheter | Umbilicus and groin | Positive skin cultures in 9 patients (16%); 3 had positive blood cultures with the same species recovered from skin |
| Bjornson, 1982 [3] | 53 patients receiving TPN, 6 with candidemia | Prospective cohort | Not mentioned | Site of iv catheter insertion | In 2 of 6 patients with candidemia, *Candida albicans* grew from the iv catheter insertion site, subcutaneous catheter segment, and blood |
| Spebar, 1981 [4] | 452 patients with burns who had *Candida* species isolated from any source, 52 with candidemia | Retrospective | Not mentioned | Burn wound | 50% of patients with candidemia had positive burn wound cultures; no species identification provided |
| Ekenna 1993 [8] | 209 patients with burns, 16 with candidemia | Retrospective | Not mentioned | Burn wound | Burn wound culture positive for *Candida* species was not predictor of candidemia by multivariate analysis; large burn size was a risk factor for candidemia by multivariate analysis |
| Gut and skin | | | | | |
| Sheridan, 1995 [21] | 962 patients with burns, 17 with candidemia | Retrospective | 1 positive blood culture, source of blood collection not mentioned | Respiratory tract, wound, stool, and urine | All patients with candidemia had the same species isolated from the wound; 35% had the same species isolated from the stool; colonization at multiple sites was associated with candidemia |
| Karabinis, 1988 [22] | 30 patients with cancer who had candidemia and 58 controls | Retrospective, case-control | 2 positive blood cultures, recovered within 72 h of each other (source of blood collection not mentioned) | Skin, urine, oropharynx, and feces | Fecal and oral colonization were risk factors for candidemia by univariate analysis; colonization from $\geqslant$1 site was a risk factor by multivariate analysis. |
| Huang, 1998 [23] | 116 low–birth-weight infants in neonatal ICU, 3 with candidemia | Prospective cohort | 1 positive blood culture from peripheral vein plus clinical signs of infection | Oropharynx, rectum, axilla, groin, urine, and tracheal tube aspirate | Only 1 of 3 patients with candidemia (*C. albicans*) was colonized (4 sites, not specified) by the same species |
| Pagano, 1999 [24] | 76 patients with candidemia who had hematological malignancies | Retrospective | 1 positive blood culture from peripheral vein or an iv catheter plus clinical signs of infection | Nasal, pharyngeal, rectal, urinary, and skin swabs | Colonization by *Candida* species (any site) was a risk factor for candidemia by multivariate analysis |
| El-Mohandes, 1994 [25] | 82 neonates in NICU, 4 with candidemia due to *C. parapsilosis* | Prospective cohort | 1 positive blood culture from peripheral vein plus clinical signs of infection | Stool, gastric aspirate, and skin (retroauricular) | *C. parapsilosis* was predominant in gastric and stool cultures; positive skin cultures were always preceded by positive stool cultures; all 4 patients with *C. parapsilosis* fungemia had rectal colonization with the same species |
| Reef, 1998 [26] | 64 neonates, 1 with candidemia due to *C. albicans* | Prospective cohort | Not mentioned | Swabs from oropharynx, umbilicus, groin, and iv site | Isolates from mouth, umbilicus, and groin showed DNA patterns that were identical to the blood isolate (RFLP and REA) |
| Gut | | | | | |
| Bow, 1995 [10] | 138 patients with AML, 16 with hematogenous candidemia | Prospective cohort | Not mentioned | Nasal, oral, and anal swabs and urine | Number of sites colonized by *Candida* species was a risk factor for invasive candidiasis by univariate but not multivariate analysis |

| | | | | | |
|---|---|---|---|---|---|
| MacFie, 1999 [14] | 279 patients undergoing laparotomy, 1 patient with candidemia | Prospective cohort | Not mentioned | Gastric aspirate and mesenteric lymph nodes | *Candida* species was the most frequent isolate in gastric aspirates (54%); the same *Candida* species was recovered from blood and gastric aspirate in 1 patient. |
| Chryssanthou, 1998 [11] | 277 patients with neutropenia, 3 with candidemia | Retrospective | 1 positive blood culture, source of blood collection not mentioned | Throat, urine, and feces | All 3 patients with candidemia had positive stool cultures for the same species |
| Pierro, 1996 [15] | 94 infants receiving TPN, 1 with candidemia | Prospective cohort | 1 positive blood culture (iv catheter or peripheral vein) plus clinical signs of infection | Oral and anal swabs | The same *Candida* species was recovered from blood and anal swab |
| Pittet, 1994 [16] | ~650 patients admitted to surgical and neonatal ICUs | Prospective cohort | 1 positive blood culture (peripheral vein or iv catheter) plus histological documentation of invasive candidiasis or endophtalmitis, or 2 positive blood cultures from peripheral vein or 1 positive blood culture from peripheral vein and 1 from iv catheter, both with identical species | Oropharynx or trachea and stomach | Intensity of colonization was a risk factor for candidemia by multivariate analysis (species not mentioned) |
| Martino, 1989 [12] | 424 patients with neutropenia | Retrospective analysis | 2 positive blood cultures from peripheral vein; if blood sample was taken from an iv catheter, candidemia was considered present if clinical signs of infection persisted after catheter removal | Nasal, oral vaginal, and anal swabs, urine, stool, and sputum | Colonization at multiple, noncontiguous sites was associated with increased risk for hematogenous candidiasis |
| Martino, 1994 [13] | 139 patients with neutropenia | Prospective cohort | 1 positive blood culture from peripheral vein; if blood sample was taken from an iv catheter, candidemia was considered present if clinical signs of infection persisted after catheter removal | Nasal, oral vaginal, and anal swabs, urine, stool, and sputum | Invasive candidiasis occurred more frequently in patients colonized at multiple, noncontiguous sites |
| Colombo, 1996 [17] | 1 AIDS patient with *C. albicans* candidemia | Case report | Not mentioned | Oral and anal swabs and urine | Blood, urine, oral cavity, and stool strains showed identical DNA profiles (PFGE) |
| Reagan, 1990 [18] | 16 patients with positive blood and surveillance cultures (various sites) | Prospective cohort | Not mentioned | Oral swab, urine, and stool | 5 patients with blood and stool cultures positive had strains available for testing and showed identical DNA patterns (RED with Southern hybridization) |
| Klempp-Selb, 2000 [19] | 6 patients with candidemia | Prospective | 1 positive blood culture, source of blood collection not mentioned | Genital swabs, stool, urine, and tracheal secretion or sputum | Stool culture was available for 2 patients; 1 had similar DNA pattern in blood and stool (PFGE) |
| Saiman, 2000 [20] | 2847 patients in NICU, 35 with candidemia | Prospective cohort | 1 positive blood culture, source of blood collection not mentioned | Perianal and rectal swabs | *C. albicans* (63%), *C. parapsilosis* (29%); all 14 blood and colonization strains available for testing (species not specified) showed identical DNA pattern (PFGE); colonization preceded candidemia in 15 of 35 patients |

**NOTE.** AML, acute myeloid leukemia; ICU, intensive care unit; NICU, neonatal intensive care unit; PFGE, pulsed-field gel electrophoresis; REA, restriction enzyme analysis; RED, restriction endonuclease digestion of chromosomal DNA; RFLP, restriction-fragment length polymorphism; TPN, total parenteral nutrition.

**Table 2. Evaluation of density and sequence of colonization and molecular-relatedness studies in specific patient populations.**

| Study subject | Patients with neutropenia | Neonates | Surgical patients | Patients with burns |
|---|---|---|---|---|
| Density of colonization | | | | |
| Gut | Yes [10, 12, 13, 22] | Yes [16] | Yes [16] | NAS |
| Skin | Yes [22] | NAS | NAS | NAS |
| Sequence of colonization and subsequent infection | | | | |
| Gut | Yes [14, 18, 22] | Yes [16, 20, 26[a]] | NAS | NAS |
| Skin | NAS | NAS | NAS | NAS |
| Molecular studies | | | | |
| Gut | Yes [18] | Yes [20, 26[a]] | NAS | NAS |
| Skin | NAS | [26][a] | NAS | NAS |

**NOTE.** NAS, no available studies.

[a] Relationship of the infection to the site was possible: 1 patient had colonization of gut and skin, but there was not a study of sequence of colonization to identify primary source.

(nose, pharynx, rectum, urine, or skin) as a risk factor for candidemia by multivariate analysis.

***Molecular-relatedness studies.*** Saiman et al. [20] prospectively evaluated 2847 neonates with weekly swabs of the perianal and rectal areas. Among 35 patients with candidemia, gut colonization preceded hematogenous infection in 15 patients. By use of pulsed-field gel electrophoresis (PFGE), all blood and gut strain pairs exhibited identical DNA patterns.

Reagan et al. [18] prospectively surveyed patients admitted to the bone marrow transplant and hematological malignancy units with weekly cultures of samples of the pharynx, urine, and stool. Sixteen patients had positive surveillance cultures and subsequently developed candidemia. In 5 patients, the gut was the colonizing site, and in all 5 cases, both colonizing and infecting strains had the same DNA pattern when tested by restriction endonuclease digestion of chromosomal DNA with Southern hybridization.

Klempp-Selb et al. [19] identified 2 patients with candidemia in whom stool cultures were obtained. In 1 of these 2 patients, the DNA patterning by use of PFGE was similar for blood and stool isolates.

Colombo et al. [17] reported an HIV-positive patient who developed a *C. albicans* fungemia. Oral, anal, and urine samples were obtained for culture, which yielded the same *Candida* species. By use of PFGE, those authors observed identical DNA profiles of the colonizing and infecting strains.

***Density and sequence of colonization and infection.*** The gut origin of candidemia is supported by the findings that the density of colonization from gut sources is a good predictor of subsequent candidemia [10, 12, 13, 16, 22] and that gut colonization precedes hematogenous candidiasis [14–16, 18, 20, 25, 35].

## Evaluation of Specific Patient Populations

The patient populations of the 21 studies reviewed were clustered in 4 major categories: patients with neutropenia who had cancer [10–13, 22, 24], newborns [9, 15, 16, 20, 23, 25, 26], surgical patients [14, 16], and patients with burns [4, 8, 21]. We analyzed 3 factors that may help identify the source of candidemia in these patient populations: density of colonization, sequence of colonization and subsequent infection, and molecular-relatedness of colonizing and infecting strains. Data in patients with neutropenia and neonates strongly suggest, on the basis of density and sequence of colonization and supporting molecular-relatedness studies, that the gut is the likely source of infection [10, 12, 13, 16, 18, 20, 22, 25]. On the other hand, the paucity of data in the surgical and burn population precludes any conclusion regarding the primary source of the infection in these settings (table 2).

## Application of Koch's Postulates to the Skin and Gut Hypotheses

We applied the Koch's postulates to further determine the strength of the relationship between candidemia and its source (table 3). All postulates were fulfilled for the gastrointestinal tract origin of candidemia, but not for the cutaneous origin. The postulates included (1) development of candidemia after the inoculation of the organism at the likely source of infection (animal models and experiment in a human volunteer) [28–35], (2) recovery of *Candida* species from the source in almost every case of candidemia [10–13, 16–22, 25], (3) eradication of *Candida* species from the likely source results in reduction of the incidence of candidemia (antifungal prophylaxis studies) [37], (4) demonstration of the sequence of colonization at the likely source and subsequent development of candidemia [16,

**Table 3. Koch's postulates adapted to source(s) of candidemia.**

| Postulate | Skin | Gastrointestinal tract |
|---|---|---|
| Development of candidemia after the inoculation of the organism at the likely source of natural infection | | |
| Experimental | NAS | Yes [28–34] |
| Clinical | NAS | Yes [35] |
| Eradication of *Candida* species from the likely source results in reduction of the incidence of candidemia | NAS | Yes [37] |
| Sequence of colonization at likely source and subsequent development of candidemia | NAS | Yes, with molecular studies [18, 25]; yes, but without molecular studies [14–16, 20, 35] |
| Density of colonization at likely source and development of candidemia | NAS | Yes [10–13, 16] |
| Recovery of *Candida* species from the source in almost every case of candidemia | Yes, but without molecular studies [3, 4, 21] | Yes, with molecular studies [20]; yes, but without molecular studies [10–13, 16–22, 25] |
| Supporting molecular-relatedness studies | [26][a] | Yes [17–20, 26[a]] |

**NOTE.** NAS, no available studies.

[a] Relationship of the infection to the site was possible: 1 patient had colonization of gut and skin, but there was not a study of sequence of colonization to identify primary source.

18, 20, 25], (5) demonstration of the influence of the density of colonization at the likely source and the development of candidemia [12, 13, 16, 22], and (6) supporting molecular-relatedness studies [17–20, 26].

## DISCUSSION

Our review led us to 2 conclusions. First, the data on the source of candidemia is limited to a few studies. Second, and most important, our review suggests an endogenous, gastrointestinal origin for candidemia, as evidenced by experimental [28–35], clinical [10–16, 18, 20, 22, 25, 35], and molecular-relatedness studies [17–20], and this is further supported by fulfillment of Koch's postulates (table 3). Additional arguments that support the gut origin include the presence of extensive gastrointestinal tract involvement in disseminated candidiasis [38], the identification of gastrointestinal colonization as a risk factor for candidemia [16], and the efficacy of antifungal prophylaxis in patients with cancer in preventing hematogenous candidiasis by eliminating or reducing colonization by *Candida* species [37].

The cutaneous origin of candidemia is suggested in *C. parapsilosis* infections. A central venous catheter is a risk factor for candidemia [22, 39, 40]. Because *C. parapsilosis* is frequently recovered from skin samples [41] and candidemia with this organism occurs more frequently in patients with central venous catheters [42], it is tempting to speculate that contamination of skin near the insertion site of a venous catheter leads to venous catheter colonization, biofilm production [43], and subsequent fungemia. However, the gut and not the skin appears to be the primary source for this infection, as shown in the study by El-Mohandes et al. [25]. In that study, stool colonization by *C. parapsilosis* was present in all patients, and a clear-cut sequence of colonization (stools followed by skin) was observed.

The data used to support skin as the source of candidemia are surprisingly incomplete. However, and although it appears that skin may not be an important source of infection in neonates and in patients with neutropenia, it is possible that this site plays an important role as a primary source in other patient populations, such as patients with burns. Indeed, extensive burn wounds may be colonized and infected with *Candida* species, which increases the risk of candidemia [8]. In addition, the limited power of a literature review and the paucity of the data available to support a cutaneous source of candidemia cannot exclude the potential role of skin as a source for candidemia. Indeed, septic thrombophlebitis and candidemia acquired from total parenteral nutrition or from contamination of skin (by stools colonized by *Candida* species) at vascular insertion sites do suggest a skin origin. Alternatively, these infections may result from contamination of a deep vein thrombus by candidemia that originated from the gut.

If confirmed by carefully conducted prospective clinical studies, our findings have implications for the clinical management of candidemia. Because the gut and not the skin may be the primary source of candidemia, attempts aimed at reducing gut colonization by *Candida* species may have a favorable impact in reducing the incidence of candidemia. Indeed, studies in patients with neutropenia who are at high risk for candidal infections have proved the efficacy of this strategy [37]. By contrast, and although formally recommended by experts in

this field [44], the automatic removal of all vascular catheters to treat all cases of candidemia should be reevaluated, particularly given that successful therapy of some cases of candidemia without vascular catheter removal is possible [45].

Finally, the most rigorous approach to confirm or refute our hypothesis is the conduct of carefully planned prospective clinical trials. These trials need to use appropriate definitions of candidemia, obtain surveillance cultures from various sites, including skin and gut, test density and sequence of colonization, and perform molecular-relatedness studies. In addition, prospective randomized studies should be performed to address the question of vascular catheter removal in the setting of candidemia.

In conclusion, the available data suggest that the source of candidemia has not been well studied and that the gut may be an important source. Additional studies are needed to confirm or refute our findings and to further evaluate the role of the skin as a potential source of this infection.

## References


1. Beck-Sagué CM, Jarvis WR. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980–1990. The National Nosocomial Infections Surveillance System. J Infect Dis **1993**; 167:1247–51.
2. Cole GT, Halawa AA, Anaissie EJ. The role of the gastrointestinal tract in hematogenous candidiasis: from the laboratory to the bedside. Clin Infect Dis **1996**; 22(Suppl 2):S73–88.
3. Bjornson HS, Colley R, Bower RH, Duty VP, Schwartz-Fulton JT, Fischer JE. Association between microorganism growth at the catheter insertion site and colonization of the catheter in patients receiving total parenteral nutrition. Surgery **1982**; 92:720–7.
4. Spebar MJ, Pruitt BA. Candidiasis in the burned patient. J Trauma **1981**; 21:237–9.
5. Ang BS, Telenti A, King B, Steckelberg JM, Wilson WR. Candidemia from a urinary tract source: microbiological aspects and clinical significance. Clin Infect Dis **1993**; 17:662–6.
6. McNeil MM, Lasker BA, Lott TJ, Jarvis WR. Postsurgical *Candida albicans* infections associated with an extrinsically contaminated intravenous anesthetic agent. J Clin Microbiol **1999**; 37:1398–403.
7. Bretagne S, Costa JM, Besmond C, Carsique R, Calderone R. Microsatellite polymorphism the promotor sequence of the elongation factor 3 gene of *Candida albicans* as the basis for a typing system. J Clin Microbiol **1997**; 35:1777–80.
8. Ekenna O, Sherertz RJ, Bingham H. Natural history of bloodstream infections in a burn patient population: the importance of candidemia. Am J Infect Control **1993**; 21:189–95.
9. Shattuck KE, Cochran CK, Zabransky RJ, Pasarell L, Davis JC, Malloy MH. Colonization and infection associated with *Malassezia* and *Candida* species in a neonatal unit. J Hosp Infect **1996**; 34:123–9.
10. Bow E, Loewen R, Cheang MS, Schacter B. Invasive fungal disease in adults undergoing remission-induction therapy for acute myeloid leukemia: the pathogenetic role of antileukemic regimen. Clin Infect Dis **1995**; 21:361–9.
11. Chryssanthou E, Kalin M, Engervall P, Petrini B, Bjorkholm M. Low incidence of candidemia among neutropenic patients treated for hematological diseases. Scand J Infect Dis **1998**; 30:489–93.
12. Martino P, Girmenia C, Venditti M, et al. *Candida* colonization and systemic infection in neutropenic patients. Cancer **1989**; 64:2030–4.
13. Martino P, Girmenia C, Micozzi A, De Bernardis F, Boccanera M, Cassone A. Prospective study of *Candida* colonization, use of empiric amphotericin B and development of invasive mycosis in neutropenic patients. Eur J Clin Microbiol Infect Dis **1994**; 13:797–804.
14. MacFie J, O'Boyle C, Mitchell CJ, Buckley PM, Johnstone D, Sudworth P. Gut origin of sepsis: a prospective study investigating associations between bacterial translocation, gastric microflora, and septic morbidity. Gut **1999**; 45:223–8.
15. Pierro A, van Saene HKF, Donnell SC, et al. Microbial translocation in neonates and infants receiving long-term parenteral nutrition. Arch Surg **1996**; 131:176–9.
16. Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. *Candida* colonization and subsequent infections in critically ill surgical patients. Ann Surg **1994**; 220:751–8.
17. Colombo AL, Branchini ML, Geiger D, Schmidt AL, Pignatari ACC, Fischman O. Gastrointestinal translocation as a possible source of candidemia in an AIDS patient. Rev Inst Med Trop Sao Paulo **1996**; 38: 197–200.
18. Reagan DR, Pfaller MA, Hollis RJ, Wenzel RP. Characterization of the sequence of colonization and nosocomial candidemia using DNA fingerprinting and a DNA probe. J Clin Microbiol **1990**; 28:2733–8.
19. Klempp-Selb B, Rimek D, Kappe R. Kariotyping of *Candida albicans* and *Candida glabrata* from patients with *Candida* species. Mycoses **2000**; 43:159–63.
20. Saiman L, Ludington E, Pfaller M, et al. Risk factors for candidemia in neonatal intensive care unit patients. Pediatr Infect Dis J **2000**; 19: 319–24.
21. Sheridan RL, Weber JM, Budkevich LG, Tompkins RG. Candidemia in the pediatric patient with burns. J Burn Care Rehabil **1995**; 16:440–3.
22. Karabinis A, Hill C, Leclercq B, Tancrede C, Baume D, Andremont A. Risk factors for candidemia in cancer patients: a case-control study. J Clin Microbiol **1988**; 26:429–32.
23. Huang YC, Li CC, Lin TY, et al. Association of fungal colonization and invasive disease in very low birth weight infants. Pediatr Infect Dis J **1998**; 17:819–22.
24. Pagano L, Antinori A, Ammassari A, et al. Retrospective study of candidemia in patients with hematological malignancies: clinical features, risk factors and outcome of 76 episodes. Eur J Haematol **1999**; 63:77–85.
25. El-Mohandes AE, Johnson-Robbins L, Keiser JF, Simmens SJ, Aure MV. Incidence of *Candida parapsilosis* colonization in an intensive care nursery population and its association with invasive fungal disease. Pediatr Infect Dis J **1994**; 13:520–4.
26. Reef SE, Lasker BA, Butcher DS, et al. Nonperinatal nosocomial transmission of *Candida albicans* in a neonatal intensive care unit: prospective study. J Clin Microbiol **1998**; 36:1255–9.
27. Odds FC. Pathogenesis of candidosis. In: Odds FC, ed. Candida and candidosis. 2d ed. Philadelphia: Bailliere Tindall, **1988**:252–78.
28. Myerowitz RL. Gastrointestinal and disseminated candidiasis: an experimental model in the immunosuppressed rat. Arch Pathol Lab Med **1981**; 105:138–43.
29. Sandovsky-Losica H, Barr-Nea L, Segal E. Fatal systemic candidiasis of gastrointestinal origin: an experimental model in mice compromised by anti-cancer treatment. J Med Vet Mycol **1992**; 30:219–31.
30. Field LH, Pope LM, Cole GT, Guentzel MN, Joe L. Persistence and spread of *Candida albicans* after intragastric inoculation of infant mice. Infect Immun **1981**; 31:783–91.
31. Umenai T, Kono S, Ishida N. Systemic candidiasis from *Candida albicans* colonizing the gastrointestinal tract of mice. Experientia **1979**; 35:1331–2.
32. Kinsman OS, Pitblado K. *Candida albicans* gastrointestinal colonization and invasion in the mouse: effect of antibacterial dosing, antifungal therapy and immunosuppression. Mycoses **1989**; 32:664–74.
33. de Repentigny L, Phaneuf M, Mathieu LG. Gastrointestinal colonization and systemic dissemination by *Candida albicans* and *Candida tropicalis* in intact and immunocompromised mice. Infect Immun **1992**; 60:4907–14.
34. Ekenna O, Sherertz RJ. Factors affecting colonization and dissemina-

tion of *Candida albicans* from the gastrointestinal tract of mice. Infect Immun **1987**; 55:1558–63.
35. Krause W, Matheis H, Wulf K. Fungaemia and funguria after oral administration of *Candida albicans*. Lancet **1969**; 1:598–9.
36. Calandra T, Bille J, Schneider R, Mosimann F, Francioli P. Clinical significance of *Candida* isolated from peritoneum in surgical patients. Lancet **1989**; 2:1437–40.
37. Menichetti F, Del Favero A, Martino P, et al. Preventing fungal infection in neutropenic patients with acute leukemia: fluconazole compared with oral amphotericin B. The GIMEMA Infection Program. Ann Intern Med **1994**; 120:913–8.
38. Walsh TJ, Merz WG. Pathologic features in the human alimentary tract associated with invasiveness of *Candida tropicalis*. Am J Clin Pathol **1986**; 85:498–502.
39. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Risk factors for hospital-acquired candidemia: a matched case-control study. Arch Intern Med **1989**; 149:2349–53.
40. Bross J, Talbot GH, Maislin G, Hurwitz S, Strom BL. Risk factors for nosocomial candidemia: a case-control study in adults without leukemia. Am J Med **1989**; 87:614–20.
41. McGinley KJ, Larson EL, Leyden JJ. Composition and density of microflora in the subungual space of the hand. J Clin Microbiol **1988**; 26:950–3.
42. Abi-Said D, Anaissie E, Uzum U, Raad I, Pinzcowski H, Vartivarian S. The epidemiology of hematogenous candidiasis caused by different *Candida* species. Clin Infect Dis **1997**; 24:1122–8.
43. Branchini ML, Pfaller MA, Rhine-Chalberg J, Frempong T, Isenberg HD. Genotypic variation and slime production among blood and catheter isolates of *Candida parapsilosis*. J Clin Microbiol **1994**; 32:452–6.
44. Rex JH, Walsh TJ, Sobel JD, et al. Practice guidelines for the treatment of candidiasis. Clin Infect Dis **2000**; 30:662–78.
45. Anaissie EJ, Rex JH, Uzun O, Vartivarian S. Predictors of adverse outcome in cancer patients with candidemia. Am J Med **1998**; 104: 238–45.