nous amphotericin B lipid complex (5 mg/kg per day), which was then switched to liposomal amphotericin B (5 mg/kg per day). There was no surgical intervention. For the first 7 days of hospitalization, the patient remained unwell in the intensive care department, with ongoing fever, profuse diarrhea, and abdominal tenderness. There was then a steady recovery. After 3 weeks, the patient had stabilized and had no gastrointestinal symptoms. Amphotericin B lipid preparations were administered for a total of 6 weeks. The patient remained healthy at follow-up 3 months later.

Gastrointestinal mucormycosis is an uncommon disease. It has most often been described in patients with diarrhea and malnutrition, infants with low birth weight, patients receiving peritoneal dialysis, and patients with solid organ transplants [1, 2]. It occurs most commonly in the stomach (60% of cases) and the colon (30% of cases), with half of the colonic cases occurring in the cecum and ascending colon [3]. The infection is thought to be acquired through direct ingestion of the pathogen [4]. The case presented here illustrates the rapid clinical onset and rapid clinical deterioration with which gastrointestinal mucormycosis often presents.

*Mucor indicus* (previously known as *Mucor rouxii*) has been reported to cause human disease 4 times previously [4–7]. Three of these cases involved the gastrointestinal tract, suggesting a possible predilection of this particular species for the gastrointestinal tract. Two of the 4 patients were immunocompetent, and 3 survived the infection. To the best of our knowledge, this is the first reported case of mucormycosis fungemia demonstrated by blood culture results.

The mortality rate for all reported cases of gastrointestinal mucormycosis is 85%. In 40% of reported cases, gastrointestinal mucormycosis infection was disseminated, and this was associated with >90% mortality. Optimal treatment has not been established, but the combination of surgery and amphotericin B therapy may be better than either of these alone [1, 8]. This case demonstrates the uncommon situation of gastrointestinal *Mucor indicus* infection presenting with fungemia, followed by successful treatment with intravenous amphotericin B lipid preparations but not surgery.

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Small-Colony Variants of Staphylococcus aureus

Sir—The case report by Spanu et al. [1] involving recurrent ventricular shunt infection with small-colony variants of *Staphylococcus aureus* (SCV-SA) calls attention to many of the important aspects of these organisms, including their tendency to cause persistent infection, particularly in association with foreign bodies; the need for prolonged incubation with enriched media; and the lack of reliability of many commercially available systems to identify and characterize the variants. However, a number of important issues need to be reconsidered.

One consideration is that it is misleading to refer to these organisms as phenotypic variants. Although it is true that SCV-SA display a number of different phenotypic characteristics, most prominently the production of small colonies on solid media that permit growth of normal-sized colonies, the fact that they do not revert en masse to larger colonies when grown on such media in the absence of a selecting agent indicates that they have genetic changes. Results of experiments done many years ago using methicillin as the selecting agent indicated that the small colonies bred true with serial passage of isolated colonies on solid media [2]. However, reversion to organisms capable of producing normal-sized colonies did occur. Frequently, the revertants appeared as outgrowths of a small colony. After 1 day of additional incubation, the revertants sometimes completely encased the small colony. One wonders whether Spanu and colleagues observed similar findings with their strain. Failure to observe revertants is consistent with the idea that the small-colony attribute resulted from a deletion rather than a point mutation. Although the authors state that the SCV-SA are nonpigmented, SCV-SA selected with methicillin were usually hyperpigmented. The revertants lost the hyperpigmentation.

Another consideration is whether the
SCV-SA observed by Spanu et al. [2] are methicillin-resistant S. aureus (MRSA). The authors demonstrated that their strain contained the mecA gene. However, no data were presented to indicate that the gene was being expressed. Of particular interest is the question of whether their strain of SCV-SA had the high levels of methicillin resistance characteristic of SCV of heteroresistant MRSA. For a typical heteroresistant MRSA strain, the majority of colony forming units could grow on media with a methicillin concentration of 4 µg/mL. But the SCV-SA could grow on media with a methicillin concentration as high as 1000 µg/mL.

A final point is that the SCV-SA were isolated from the patient after receipt of ciprofloxacin (the temporal relationships between other antibiotics administered and the isolation of the SCV-SA are unclear). It would be interesting to determine whether ciprofloxacin could select for SCVs from the original S. aureus isolate. In addition to methicillin, a variety of compounds can be used to select for SCV-SA, including other inhibitors of cell-wall synthesis (vancomycin, cycloserine, and bacitracin), other antibiotics (e.g., chloramphenicol and kanamycin), crystal violet, and BaCl₂. In some instances, selection with agents with different mechanisms of action (crystal violet and methicillin) resulted in SCV-SA with increased resistance to unrelated compounds (S.J. Seligman, unpublished data).

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References


Reply to Seligman

Sir—We thank Dr. Seligman [1] for his interest in our article [2]. Our ability to respond to the issues he raises is limited by the fact that we have been unable to access a copy of Dr. Seligman’s 1966 article [3], which is the basis for most of his questions. Nonetheless, we can provide some of the information he has requested.

First, we did not intend to exclude, with the term “phenotypic variant,” the possibility that single-colony variants of Staphylococcus aureus (SCV-SA) are genotypically different from the parent S. aureus strain. There are numerous reports in the literature indicating that the phenotypic peculiarities of SCV-SA are indeed the result of genetic alterations [4–6], although the mechanisms underlying these alterations may be highly complex [7].

Our strain produced slow-growing, pinpoint, nonpigmented, nonhemolytic colonies on Columbia agar, and no reversion was noted with serial passage of isolated colonies on this medium. In contrast, normal growth was noted on Schaedler agar (48 h at 35°C with CO₂). Our SCV-SA strain was unequivocally nonpigmented, which is also consistent with information in the literature [4, 5].

As for the expression of methicillin resistance by the organisms we observed, the oxacillin MIC we reported (0.5 mg/L) is consistent with a heteroresistant phenotype involving variable mec expression [2]. In strains with heteroresistance (regardless of whether S. aureus is metabolically normal or a SCV), the methicillin MIC for the majority of cells will be relatively low, but under antibiotic pressure, the entire culture can be overgrown by those few cells that fully express mec. Therefore, the simple presence of the mec gene in clinical isolates of S. aureus, including SCVs, represents a potential threat to the success of β-lactam therapy, regardless of whether the gene is expressed during in vitro testing. Clinically speaking, the main question is, thus, whether an S. aureus strain carries the mecA gene. This is particularly true for SCV-SA. Because of the slow growth of SCV-SA, PCR detection of mecA is the only reliable way to identify methicillin resistance [8].

Various antimicrobials, including aminoglycosides and trimethoprim-sulfamethoxazole [4], can select for SCV-SA. Three months before the emergence of our patient’s infection, she was discharged after a 2-month period of hospitalization, during which she had received various antimicrobials, including (but not limited to) ciprofloxacin and gentamicin. Mitsuyama et al. [9] showed that the ability of a quinolone to induce emergence of the SCV phenotype is related to the drug’s chemical structure: agents with a nitrogen-bonded piperazinyl group at the C-7 position of the quinoline, pyridopyrimidine, or naphthyridine nucleus (e.g., ciprofloxacin) are unable to induce SCV emergence. Furthermore, Pan et al. [10] showed that quinolone-derived small-colony mutants differ from the majority of clinical strains of SCV-SA because they are not auxotrophic for hemin, menadione, or thymidine. Such SCV-SA strains thus emerge because of the effects of adenine triphosphate production by mutant genes in other pathways.

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