Reply to Dr. Chandrasekar (Clin Infect Dis 2001; 32: 320–1) and Drs. Marr and Boeckh (Clin Infect Dis 2001; 32:321)

Sr—The point raised by Dr. Chandrasekar [1] regarding treatment with fluconazole is appropriate, and we thank him for reminding us about the 1997 guidelines from the Infectious Diseases Society of America (IDSA) on treatment of fever in patients with neutropenia [2]. Although in our guidelines the “Treatment Options” subsection of the section on fever and neutropenia said that fluconazole therapy was “often inappropriate,” it is not always inappropriate, and further elaboration on this point is useful. Not all neutropenic patients have the same risk of infection caused by Aspergillus or other filamentous fungi, and fluconazole could be used in carefully selected circumstances. As a consequence, we would amend the guidelines to include the following Key Recommendation:

Fluconazole (400 mg/day) has been used successfully in selected patients (AI) [3–5], and could be considered as an alternative strategy if (1) the patient is at low risk for infection due to Aspergillus or other filamentous fungi, (2) the patient lacks any findings that suggest that the current fever might be due to Aspergillus or other filamentous fungi (studies should include high-quality CT of the chest plus any other clinically indicated sites), (3) local epidemiology suggests that the patient is at a low risk for infection with azole-resistant isolates of Candida species, and (4) the patient has not received an azole antifungal agent as prophylaxis.

Dr. Chandrasekar also comments on the dosage of amphotericin B to be used for the treatment of aspergillosis. The comments in guidelines for the treatment of candidiasis [6] specifically address fever of unknown etiology, and the stated dosages of amphotericin B are the most commonly used dosages for patients with such fever. As discussed in the accompanying paper on guidelines for aspergillosis [7], maximum tolerated dosages of amphotericin B are indeed appropriate if aspergillosis is proven or strongly suspected.

Dr. Chandrasekar closes his comments with an aside about the timing of initiation of antifungal therapy. We recommended that the doctor consider starting antifungal therapy if a patient with fever fails to respond despite having received 4–6 days of suitable antibacterial therapy (i.e., on or after day 5 of persistent fever); this allows for sufficient time for resolution of a fever caused by a bacterial infection. It also follows the design of most major trials in this area, and is consistent with the IDSA’s recommendation to start therapy during days 5–7, a recommendation that was published in the 1997 IDSA guidelines on the treatment of fever in patients with neutropenia [2]. The effect of prior antifungal prophylaxis on this recommended treatment is currently unknown, as is the potential impact of better culture- and non-culture-based techniques for the diagnosis of fungal infections. This latter theme is echoed by Marr and Boeckh [8].

We also thank Drs. Marr and Boeckh for the reminder regarding the importance of risk-stratified thinking, and we agree with the belief that not all forms of immunosuppression are created equal [9]. The very recently published data on the possible benefit of long-term fluconazole prophylaxis were not available at the time that the guidelines were written; the data will be incorporated into their next revision. The aforementioned 1997 IDSA guidelines on the treatment of fever in patients with neutropenia [2] comment on the issue of prophylaxis from a host-directed vantage point.

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References


7. Stevens DA, Kan VL, Judson MA, et al. Prac-
Extra-intestinal Salmonella Infections: The Significance of spv Genes

Str—I have to differ with Dr. Chiu and colleagues regarding both their conclusions about the importance of the virulence plasmid in cases of extraintestinal Salmonella infections in humans [1] and their interpretation of our study [2]. A very small number of serotypes of Salmonella serotypes, most of which are host adapted to a genus of animals, carry virulence plasmids [3]. The plasmids differ in size according to their serotype specificities, but all virulence plasmids have in common a highly conserved 8.2-kb region (the spv operon) that is responsible for the virulence phenotype [4]. Chiu et al. imply that we used an imprecise method to identify isolates that carry virulence plasmids. We used a 4-kb probe from the center of the highly conserved spv operon to detect the homologous genes in the Salmonella serotype Typhimurium plasmid. The differences between virulence plasmids from the different serotypes that Chiu et al. cited are outside the conserved spv region and were not in our probe.

The presence of a virulence plasmid greatly enhances the virulence of those Salmonella serotypes in experimental infections in mice and in the animals that are the natural hosts for these bacteria [5–9]. Functionally, these plasmids are interchangeable [10]. We agree that chromosomal genes also play a necessary role in systemic infections, because many Salmonella serotypes cannot be made mouse virulent by the insertion of a virulence plasmid [11].

There is general agreement that the presence or absence of virulence plasmids is irrelevant for the pathogenesis of Salmonella gastroenteritis in humans. We have to rely on epidemiological studies to determine whether virulence plasmids are important in the pathogenesis of invasive nontyphoid Salmonella infections. Is there a correlation between invasiveness and the presence of the plasmid? This cannot be answered by the study of serotypes such as Salmonella serotype Dublin and Salmonella serotype Choleraesuis, because all clinical isolates of those serotypes carry a virulence plasmid. It also cannot be answered if most or all of the fecal isolates of S. Typhimurium or S. serotype Enteritidis carry virulence plasmids; this was the case in the study by Chiu et al. In their study of Salmonella isolates obtained from patients from a single municipality on the island of Taiwan, 85% of the fecal isolates of S. Typhimurium had virulence plasmids. Given this, it is not surprising that they did not find that a higher percentage of blood isolates had plasmids. It is possible that most of their isolates were, in fact, one or a few clones, because the isolates were collected from a small geographic area during a single year. To avoid this pitfall, we studied Salmonella serotype Typhimurium that had been collected from widely separated areas of the United States during a period of 9 years, to be sure that we were not testing epidemiologically related isolates. We were able to show that fewer fecal than blood isolates carried a virulence plasmid (42% vs. 76%). Montenegro et al. [12] had nearly identical results for studies of Salmonella serotype Typhimurium and S. serotype Enteritidis in animals and persons in Germany.

I believe that these studies are compatible with the hypothesis that the virulence plasmid contributes to invasiveness of nontyphoid Salmonella species. It is obvious that this hypothesis cannot explain how Salmonella serotypes Typhi and Paratyphi cause invasive disease, because neither serotype has the spv genes.

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References

11. Roudier C, Krause M, Fierer J, Guiney DG. Correlation between the presence of sequences homologous to the vir region of Salmonella dublin plasmid pSDL2 and the vir-