11. da Silva Coimbra MV, Silva-Carvalho MC, Wisplinghoff H, et al. Clonal spread of methi-

Reprints or correspondence: Dr. David P. Caffee, Box 801337, University of Virginia Health System, Charlottesville, VA 22908 (dpc5k@virginia.edu).
Clinical Infectious Diseases 2003; 37:1402–3 © 2003 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2003/3710-0026$15.00

**Why Refrigeration Paradoxically Prolongs Bacterial Survival in the Presence of Preservatives**

Str—We have read the article by Kirschke et al. [1] with interest. The reported out-
brack they discuss highlights the impor-
tance of strict attention to aseptic pro-
cedures. However, in the clinical practice, it is rather difficult to obey such procedures if they are not understood. Here we pre-
 sent an easy, supportive explanation.

The real clinical problem is that many multiple-dose formulations now contain preservatives, and refrigeration might paradoxically prolong bacterial survival in these formulations. This refrigeration-mediated effect was already recognized in 1977 [2]. Recently, it has been suggested that the prolonged survival of bacteria is due to inhibition of the activity of some preservatives at lower temperatures [1].

The activity of the preservatives is not inhibited by refrigeration, but, rather, the growth rate—and, thus, the metabolic ac-
tivity—of the microbes. The concentration of preservatives is normally very low, and, therefore, decrease of the concentra-
tion by crystallization does not occur. The idea that a decrease in temperature results in increased chemical destruction and a consequent inactivation of preservatives is contradicted by chemical laws, because chemical instability increases only with an elevation of temperature. It is the growth of microbes that is normally prevented by refrigeration, especially because of the lower level of those enzymatic activities that are involved in the multiplication process. This reflects the primary function of a refrigerator.

However, just as is the case with dis-

fectants, antiseptics, and antibiotics, pre-

servatives are antimicrobial agents, which interfere in the biochemical processes that occur during microbial growth and mul-
tiplication. All of these agents require growing and metabolizing microorgan-
isms in order to produce their antimicro-
bial effect. Microorganisms have an op-
timal growth temperature. This means that many microbes will be rapidly killed by antimicrobial agents at room temper-

ature, and will normally be killed even more effectively at 37°C, but will not be killed in the refrigerator. After injection in the patient, the antimicrobial preser-

atives, which have been adhered to by or are present inside the microbes, will leak out and become diluted. Consequently, re-

frigeration will protect the microbe inside the vial against the antimicrobial effect, and, later on, inside the patient, the mi-

crobe will multiply and spread.

In conclusion, most, if not all, anti-

microbial agents will simply not kill or inactivate microbes at low temperatures. In other words, refrigeration prolongs bac-
terial survival in the presence of preser-

atives because of the very low microbial growth rate. At room temperature, these preservatives can very efficiently inhibit specific microbial processes that are involved in multiplication.

Ger P. A. Bongaerts,1,2 and Leonie E. Jansen1,2

1Department of Medical Microbiology
and 2Nijmegen University Centre for Infectious Diseases, University Medical Centre Nijmegen, The Netherlands

**References**

2. Lehmann CR. Effect of refrigeration on bacteri
dical activity of four preserved multiple-

Reprints or correspondence: Dr. Ger P. A. Bongaerts, Dept. of Medical Microbiology, University Medical Centre Nijmegen, PO Box 9101, NL 6500 HB Nijmegen, The Netherlands (Ger.Bongaerts@mmb.umcn.nl).
Clinical Infectious Diseases 2003; 37:1403 © 2003 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2003/3710-0027$15.00

---

**Correspondence** • CID 2003;37 (15 November) • 1403