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Correspondence

A need for careful consideration of bacteriophage therapy

Sir,

We read with great interest the article by Kishor *et al*[1] on phage therapy of staphylococcal chronic osteomyelitis in experimental animal model. Bacteriophages have been used for therapy as far back as 1917 by Felix d'Herelle who after ingesting them himself administered them to a 12 yr old boy with severe dysentery[2]. Phages have been routinely used as therapeutic agents in Eastern Europe and the former Soviet Union, being administered by various routes, with only a few reported cases of severe adverse reactions[3].

PhagoBioDerm (Phage International, Georgia) is a commercial preparation containing a panel of phages against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Proteus* and *Streptococcus*[4]. The United States Food and Drug Administration has approved the use of anti-*Listeria* phage cocktails (ListShield™ and LISTEX™ P100) as food additives (poultry products and meat)[5]. Omnilytics, Inc., (US) specializes in supplying customized phage preparations for agricultural use (Omnilytics' Agriphage™), tailored against bacteria infecting plants during the growing season[6]. However, detailed research on the kinetics of phages administered to animals and humans is lacking. Available data on the pharmacokinetics of phage preparations suggest that phages can enter the bloodstream and be found in the internal organs within 10 h of administration, and can remain in the body for up to several days. Sequestration in the filtering organs would prevent the bulk of administered phages from reaching the infecting bacteria[7]. Moreover, the environment in some body compartments where bacteria reside may not allow the phages to establish themselves. Mathematical models developed by Cairns *et al*[8] have suggested that paradoxically, addition of antibiotics in parallel with phage may hamper phage efficacy. A detailed study on the effects of varying phage doses and time of administration after infection using a mouse model of vancomycin-resistant enterococci is available[9].

One should also remember that phages may harbour virulence factors or toxin genes. The determination of the complete nucleotide sequence of a *P. aeruginosa*-specific phage led to the observation that a number of the gene products bore striking similarity to functionally unknown proteins from diverse organisms[10].

Host range, phage virulence and burst size are some important parameters that need to be considered when selecting phages for therapeutic uses. Perhaps, the authors could have detailed the quantification of the phages carried out to prepare the various concentrations[1]. How were the most virulent phages determined to prepare the cocktail? Have the results of electron microscopy and molecular tests been used to help classify the isolated phages? An individual phage may have a host range of 30-40 strains of bacteria, and even bacteria from other genera. The phage cocktail prepared could have been tested *in vitro* on *S. aureus* or methicillin-resistant *S. aureus* strains before being injected into the rabbits to demonstrate host specificity. However, the concern that phages administered therapeutically might disturb the normal flora is largely unfounded as phages are highly receptor-specific, and no such data have been reported from studies elsewhere[3]. One of the possible roles for phages in the near future that can be relatively safely explored is their use as a fomite decontaminant[11].

There are several questions that arise after reading the article by Kishor *et al*[1]. An appropriate control group is essential to validate the results. Instead of the chronic osteomyelitis model group (group B), the group in which therapeutic intervention was not carried out (group A) could have been designated as the control group. The autopsy findings of the animals

have not been presented: was there bacterial invasion of the bloodstream in spite of phage therapy? Was an attempt made to isolate the administered phages from the bloodstream and various organs? Group B rabbits, which became culture negative in the eighth week, were followed up for another two months but outcome at the end of this period was not mentioned. Was there any change in them? Since results for rabbits in group B have been presented up to the eighth week, some of the rabbits in group A could have been kept alive for the same time, serving as a control for the chronic osteomyelitis group at the time of intervention.

As we look for weapons to add to the depleting arsenal against multidrug-resistant bacteria, studies such as this need to be designed well to solve several unanswered queries. Detailed research on the available options will go a long way in adding to the armamentarium to treat infections with pan-drug resistant organisms.

***Conflicts of Interest*:** None.

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