

## CASE REPORT

# Yoghurt biotherapy: contraindicated in immunosuppressed patients?

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A fatal case of *Lactobacillus rhamnosus* septicaemia after prolonged oral vancomycin for recalcitrant *Clostridium difficile* infection is reported. The patient was immunosuppressed with cyclophosphamide and steroids for Sjögren's syndrome. The administration of *Lactobacillus* spp as "biotherapy" may be hazardous in such circumstances.

Diarrhoea caused by *Clostridium difficile* is often treated with oral vancomycin. The best treatment approach for relapse is uncertain. A regimen of repeat and tapering courses, followed by pulsed treatment with oral vancomycin or oral metronidazole has proved effective.<sup>1</sup>

*Lactobacillus* spp have frequently been advocated as "biotherapy" for gastrointestinal infections<sup>2</sup> and there have been few reported complications. *Lactobacillus rhamnosus* is present in yoghurt and is a rare opportunistic pathogen.

### CASE REPORT

A 42 year old woman with a long history of Sjögren's syndrome, idiopathic renal failure, and an idiopathic axonal peripheral neuropathy causing type II respiratory failure was receiving cyclophosphamide and fludrocortisone. She developed *Staphylococcus aureus* pneumonia which responded to flucloxacillin and gentamicin (both given intravenously). Two weeks later she received oral trimethoprim for a urinary tract infection. Her respiratory condition deteriorated and she was started on intravenous ciprofloxacin and the oral cyclophosphamide was then stopped. After four days *C difficile* toxin positive diarrhoea developed and oral metronidazole was introduced. Diarrhoea continued for two weeks; oral metronidazole was switched to oral vancomycin due to poor response. A short course of live yoghurt (supermarket own brand) was given. After three weeks of oral vancomycin the diarrhoea settled and the *C difficile* toxin became undetectable.

The patient subsequently developed *Streptococcus pneumoniae* septicaemia and was treated with tazocin and gentamicin (both given intravenously). Endotracheal ventilation was required and she received hydrocortisone, fludrocortisone, and parenteral nutrition.

Central line and peripheral blood cultures grew a Gram positive bacillus. This was initially treated with tazocin, gentamicin, and vancomycin (all intravenous). Laboratory identification of this organism proved difficult, the organism's identity as a *Lactobacillus* spp was finally alluded to by the antibiogram (resistant to vancomycin) and temperature requirements for growth. Rifampicin (intravenous) was added to provide additional cover for the lactobacillus sepsis. Subsequently, her gas exchange deteriorated, she developed cardiovascular instability, tachycardia, and severe pyrexia. She suffered an asystolic cardiac arrest after four days of intensive care. The identity of the *Lactobacillus* spp was confirmed by the Public Health Laboratory Service as *Lactobacillus rhamnosus*.

### DISCUSSION

In this case the patient was critically ill, having had *S aureus* pneumonia, *C difficile* infection, pneumococcal septicaemia followed by a *L rhamnosus* septicaemia, as well as her underlying multiple medical problems. She had persistent high fevers despite antibiotic treatment. The cause of death was attributed to pneumonia due to *S pneumoniae* infection and secondary *L rhamnosus* septicaemia. The combination of live yoghurt ingestion, immunosuppressed host, and prolonged courses of multiple broad spectrum antibiotics including oral vancomycin paints a complicated picture. In this case, the microbiological link between the yoghurt eaten and the lactobacillus blood culture was not proved. It is certainly possible that the septicaemia due to the *L rhamnosus* originated from the live yoghurt consumed, and this case highlights the need to proceed with caution particularly with this kind of live therapy in heavily immunosuppressed individuals in line with existing guidelines on the use of live vaccines in immunosuppressed patients.

The report also highlights the clinical difficulties in treating persistent *C difficile* diarrhoea. Repeated or pulsed courses of either oral metronidazole or oral vancomycin may prove effective.<sup>1</sup> *Lactobacillus* spp are commonly used in some dairy products as part of the manufacturing process and have long been advocated as biotherapy for antibiotic associated diarrhoea.<sup>2-4</sup> Fermented milk products, such as yoghurts, will contain live bacteria. The bacterial strains used are frequently unnamed but *Lactobacillus* spp, *Bifidobacterium bifidum*, *Streptococcus lactis*, and *Streptococcus cremoris* are common. *L rhamnosus* strain GG has been extensively studied and widely used as biotherapy.<sup>5</sup> Although the exact mode of action of "biotherapy" remains uncertain, competition between commensals and pathogens for the same nutrients or binding sites and/or production of inhibitory metabolic products seem likely.

The human faecal flora is predominated by anaerobic non-spore forming organisms such as *Bacteroides* spp. *Lactobacillus* spp are found throughout the gastrointestinal tract, their number and species distribution depends on diet and site of sampling in the gastrointestinal tract.<sup>6</sup> Lactobacilli are one of the few Gram positive species intrinsically resistant to vancomycin.<sup>7</sup> Others include *Leuconostoc*, *Pediococcus*, and *Ersipelothrix* spp. In this case, *L rhamnosus*, a normal member of the intestinal flora and present in "live yoghurt" may have been selected by prolonged oral vancomycin treatment.<sup>8</sup> Lactobacilli are infrequent pathogens; the majority of isolates are from patients with endocarditis, the source most probably either the oral cavity, gastrointestinal tract, or female genital tract.<sup>9</sup> *Lactobacillus* septicaemia in the absence of endocarditis is rare and in a review of 55 cases, underlying conditions included cancer, organ transplantation, diabetes mellitus, and recent surgery with a mortality rate of 14%.<sup>10</sup> More recently, severe cases of septicaemia due to *Lactobacillus* spp have been reported in neutropenic patients after bowel decontamination with oral vancomycin.<sup>11</sup>

### Summary points

- *Clostridium difficile* can be treated with metronidazole or vancomycin.
- Biotherapies containing lactobacilli and saccharomyces have been advocated for antibiotic associated diarrhoea.
- A prolonged course of vancomycin carries the risk of selection of a resistant flora.
- Host immunocompetence must be considered when introducing live biotherapies.

In conclusion, the use of *Lactobacillus* spp as "biotherapy" should be carefully considered in the immunosuppressed, particularly when prolonged oral vancomycin has been administered.

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