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Review

Probiotics: a new frontier for infection control

J.V. Seale*, M. Millar

Department of Infection, Barts and The London NHS Trust, Whitechapel, London, UK

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SUMMARY

Probiotics are live micro-organisms administered to provide health benefits. Probiotics are being increasingly used in healthcare contexts both in research studies and routine practice, for example in neonatal intensive care. Currently there is a paucity of guidelines or regulations governing the mitigation of infection risks associated with the use of probiotics in clinical practice. We propose a number of recommendations to mitigate risks. These include the communication of probiotic use to appropriate stakeholders, ensuring that routine laboratories can identify and test the susceptibility of probiotic strains, assuring standards for preparation and administration, and ensuring surveillance designed to capture adverse events.

Introduction

The potential health benefits of probiotics have been recognized for more than 100 years.[1] The World Health Organization (WHO) defines probiotics as 'live microorganisms which, when administered in adequate amounts, confer a health benefit on the host'.[2] This definition acknowledges a possible role for probiotics in medical practice, but does not acknowledge that probiotics (albeit rarely) can cause disease. Over the last 10 years there has been increasing public and scientific interest in the administration of these live micro-organisms to prevent or treat disease. Twenty-three publications were retrieved from PubMed for the year 1995 using the search term 'probiotic' compared with about 200 in the year 2000 and more than 600 for the first half of 2012. Much of the focus of this research has been on the use of probiotics for the prevention or treatment of gastrointestinal conditions such as inflammatory bowel disease and inflammatory bowel syndrome.[3,4] More recent studies have suggested that the influence of probiotics extends well beyond the gut and may even extend to modulation of emotional states and neurological functioning.[5,6]

Neonatal necrotizing enterocolitis (NEC) is a gastrointestinal disease associated with a high degree of mortality and morbidity, especially in the more preterm infant. A recent systematic review by Deshpande *et al.* of 11 randomized controlled trials in 2176 infants of <34 weeks' gestation reported that enterally administered probiotics substantially reduced the risk of NEC and also death attributable to any cause.[7] This has led to the suggestion that placebo-controlled probiotic trials in infants are no longer ethical and that probiotics should be used routinely.[7,8] There are potential risks associated with the use of probiotics, a number of which have been acknowledged in the current literature.[7,9,10] Many of these risks can be directly, or indirectly, mitigated by attention to infection control practice. We consider some of the risks and associated questions relevant to the safe use of probiotics using the particular example of the vulnerable preterm infant.

Probiotic regulation

Manufacturers of probiotic supplements promote the potential association of probiotics with gut health, an image that is widely advertised in the popular media and undoubtedly underlies their success as a food supplement. International bodies including the European Food Safety Authority and WHO have made recommendations focused on the assessment of the safety of probiotics.[2,11,12] These recommendations refer to the

* Corresponding author. Address: Department of Infection, Barts and The London NHS Trust, 80 Newark Street, Whitechapel, London, UK. Tel.: +44 (0) 203 2460296; fax: +44 (0) 203 2460303.
E-mail address: Josephine.Seale@bartshealth.nhs.uk (J.V. Seale).

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use of probiotics as dietary supplements in the wider 'healthy' population and cannot be directly applied to the use of probiotics in a hospital setting.[7,9,10] The question has been raised as to whether probiotics used as a medical intervention, either in routine practice or in clinical trials, should be regulated as drugs? Probiotics are not drugs in that they cannot be chemically defined and controlled to the same extent. Probiotics are live organisms which are able to reproduce, change with time and have the potential to interact dynamically with the human host. It is these distinguishing qualities which could themselves cause adverse consequences and justify regulation.

Regulatory concerns regarding the clinical application of probiotics were emphasized following publication of the results of the PROPATRIA trial in The Netherlands wherein 24 patients in the probiotics group died compared with nine in the placebo group.[10] By contrast with the European community, the US Food and Drug Administration clearly differentiates the use and promotion of probiotics to prevent or treat disease (drugs) from their use by healthy people as dietary supplements.[13] Classifying probiotics used for medical indications as 'drugs' effectively limits their application in routine clinical practice in the USA to clinical trials and arguably will slow the development of effective probiotic interventions.[14]

What are the risks of probiotics?

Infection

The term 'healthy bacteria' is a metaphor which implies that probiotics generally contribute to health rather than disease. There are both historical and more recent examples of how things can go wrong when probiotics are used. The PROPATRIA trial mentioned above is a more recent example of probiotics contributing adversely to patient outcome. There is a historical example from neonatal practice. In the 1960s there was widespread and deliberate exposure of US neonatal units to *Staphylococcus aureus* 502A. This practice was deemed beneficial following the demonstration that colonization of patients with this organism conferred protection against more virulent strains of *S. aureus*.[15] However, the development of infection in 6% of children and one death resulted in termination of this practice and highlighted the risks associated with widespread manipulation of the natural microbial ecosystem. It is feasible that a similar scenario could occur with the routine use of probiotics despite their seemingly low virulence.[16] Bacteraemia and meningitis can be caused by probiotics and these rare events highlight the potential for disease in the immunocompromised host.[17–20] There are particular concerns about the potential for contamination of biomedical devices such as central venous catheters. There are few scenarios in clinical practice in which healthcare staff deliberately administer large numbers of bacteria (usually $>10^8$/dose) to patients and there is considerable potential for air-borne or vector-mediated contamination of devices or connections.[13]

Accidental administration

Probiotics are frequently prepared alongside other feeds in neonatal units and alongside routine food and drink in adult wards. There is potential for cross-contamination such that probiotics may accidentally be administered to the wrong patient. Probiotic bacteria may also cross-colonize individuals, a situation which has been described in neonatal intensive care units.[21,22] This scenario is particularly problematic in patients for whom uncertainties exist as to the effect of probiotics, such as those with gastrointestinal anomalies.[23] Infants with gastrointestinal anomalies have been excluded from most (if not all) probiotic trials.

Antibiotic resistance

Antibiotic resistance represents a continual threat to effective treatment. By contrast, the presence of antibiotic resistance in probiotics may be deemed advantageous by enabling probiotic survival in an intestinal environment where antibiotics are often concurrently administered.[11] This resistance is frequently intrinsic and therefore non-transmissible.[11] However, a potential danger arises whereupon resistance is due to transmissible plasmid-encoded antibiotic resistance genes which are consequently passed on to more virulent colonizing bacteria.[24] The presence of plasmids carrying antibiotic resistance in the probiotic strains *Lactobacillus fermentum* and *Lactobacillus plantarum* demonstrates this potential.[25,26] An additional concern is that probiotic bacteria may promote microbial diversity, and, in so doing, may also promote colonization with antibiotic-resistant strains.

Unquantifiable and unknown risks

The upsurge in probiotic research has occurred predominantly over the last decade and is still in its early stages with regard to determining the developmental and ecological consequences their use may have. The complexity of the bowel flora of humans precludes complete confidence in understanding the full extent of potential influences. Thus, even though probiotics may be beneficial in the short term, their longer term immunological, developmental and ecological effects as well as any interactions with other preventive and therapeutic interventions are unclear.[23] These uncertainties should not prevent probiotic interventions for individuals in whom they may be beneficial but it is important to acknowledge that there remain potential consequences of their use which are impossible to predict. These uncertainties add further weight to the need to limit exposure to probiotics to those for whom exposure is intended.

What can we do to minimize potential risks associated with probiotic use?

Given the potential risks of probiotics and their increasing use in predominantly high-risk individuals, it is important to consider means of mitigating risks. Ensuring that probiotics are used appropriately requires a detailed knowledge of the characteristics of the organism itself in conjunction with a standardized approach to their administration and surveillance. It is important to be able to recognize infection with probiotic strains, regulate preparation and administration, ensure adequate staff training and encourage appropriate audit and surveillance programmes.

Characterization, identification and sensitivity testing of probiotic strains

Probiotics predominantly belong to the genera *Lactobacillus* and *Bifidobacterium* although other species such as *Streptococcus*

spp. and *Enterococcus* spp. have been utilized in a variety of situations.[27–30] In light of the lack of consensus as to the optimal strain(s), dose and duration, it is perhaps unsurprising that limited data exist as to the microbiological characteristics of these bacteria. The differential ability of probiotic strains to cause disease or to potentially transfer antibiotic resistance genes highlights the importance of profiling each strain accurately so that those possessing such factors can be avoided.[31] Detailed bacterial identification and determining a probiotic's potential pathogenicity is likely to require the use of conventional biochemical methods in conjunction with novel molecular technologies.[12] Ideally the accurate characterization of each probiotic strain, including the conditions required for culturing them *in vitro*, should be determined by the food manufacturers prior to their use in food supplements. This profiling would then provide a basis from which routine laboratories could ensure that they had the means to isolate, identify and determine the antibiogram of an organism prior to its subsequent application in clinical trials or practice. We propose that routine laboratories should have the capacity both to identify the probiotic bacteria in current use and to carry out susceptibility testing.

Regulated preparation and administration

Probiotic preparations are often prepared in clinical environments. Preparation may require rehydration of freeze-dried powders or addition of liquid preparations to feeds. Addition of probiotics to feeds at a temperature required to maintain viability runs contrary to guidelines on the safe preparation of infant feeds.[32] Mitigation of the risks of environmental contamination, accidental exposure and subsequent colonization require stringent precautions for the preparation of probiotics. It would seem reasonable to require that the preparation of probiotics in critical care units be confined to defined areas in which environmental contamination can be monitored. Also preparation should be carried out by staff with an appreciation of potential risks and with appropriate training ideally provided by those responsible for manufacturing the probiotic strains. These precautions are broadly consistent with those that we already take, but, in some areas, go beyond current best practice such as minimizing the risks of environmental contamination or cross-colonization and minimizing exposure for those in whom this is deemed inappropriate. We propose that there should be local policies governing the safe preparation and administration of probiotics in clinical areas.

Surveillance

Personal experience suggests that many infection control professionals are not aware of the full extent to which probiotics are being used in their own hospitals. This highlights the need for increased transparency regarding the type of probiotic interventions being used in different clinical contexts. Given the potential infection control risks surrounding probiotics, surveillance of their use by the infection control team at each hospital would be beneficial and also ensure that these risks were considered at an early stage. Surveillance would ideally entail a means of recording the daily progress of patients being administered probiotics, including any adverse or beneficial consequences. In light of the increasing number of institutions utilizing probiotics, a standardized database by which to record such data would provide a means of monitoring their effects at both local and national level, the latter of which would facilitate future epidemiological study. The cross-contamination issues surrounding probiotic use also warrant surveillance of non-exposed patients residing in environments utilizing probiotics to assess for any consequences on the health of these individuals. We propose that surveillance programmes designed to identify adverse events are established particularly when probiotics are being administered to high-risk patients.

Some relevant questions

In the UK there are no specific regulations governing the use of probiotics in clinical practice. We propose that a number of questions need to be addressed by those considering or already using probiotics in the medical setting in order to focus attention on their potential risks (Box 1).

The importance of considering these questions and for regulation should not be underestimated given that an adverse event resulting from probiotic use could do irreversible harm to this emerging and potentially beneficial area of research. This possibility should not preclude the use of probiotics but does require the instigation of measures to minimize this risk. In line with the issues raised throughout this article, we recommend that the following should be adhered to when using probiotics in clinical practice (Box 2).

Box 1

Questions to be addressed when using probiotics in the clinical context

- Is there a notification process that allows relevant departments to know that probiotics are being used?
- Can the laboratory culture the strains being used?
- Are the antibiotic susceptibility profile(s) of the probiotic strains known?
- Are there patients who should not be exposed to probiotics within the environment in which probiotics are being used?
- Is there potential for contamination of equipment, intravenous solutions and foodstuffs?

Box 2

Recommendations for the use of probiotics in clinical practice

- Food companies producing probiotics should provide evidence regarding the purity of the bacterial strain(s) used and the lack of contamination of their products.
- Characterization and antibiotic sensitivities of each probiotic strain should be available prior to its utilization.
- Training of staff in the preparation and administration of probiotics should be provided by the manufacturing company.
- All relevant individuals and departments should be informed of the use of probiotics.
- The infection control team should be involved in the clinical use and surveillance of probiotics.
- Specialized preparation and storage areas should be provided on every ward utilizing probiotics.
- Patients in whom the effect of probiotics has not been assessed or is potentially detrimental should be nursed in a probiotic-free environment.

Conclusion

The expanding use of probiotics in both the commercial and clinical sectors suggests that probiotics are generally considered to be safe. There is increasing evidence of beneficial effects in a range of conditions. There are avoidable events which can be prevented by infection control actions. We have highlighted some potential considerations if we are to assure the safe application of probiotics in the clinical setting. It is hoped that increased vigilance in the utilization of probiotics will facilitate the continued exploitation of their beneficial effects while minimizing their risks.

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None declared.

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