Travellers' diarrhoea

I appreciated Dr Leder's article on travellers' diarrhoea (TD; *AFP* Jan–Feb 2015)[1] and her updated suggestions and practical management. However, I would like to challenge two points in the article.

1) That probiotic approaches for treatment and prevention are ineffective:
A Cochrane review on this very topic, while acknowledging that more research is needed, suggested that probiotics are a very promising approach and, on average, 'will shorten the symptoms duration of diarrhoea by around 25 hours, the risk of diarrhoea lasting 4 or more days by 59%, and resulted in about one fewer diarrhoeal stool on day 2 after the intervention'.[2] Another good meta-analysis concluded that up to 85% of TD cases could be prevented by probiotic approaches.[3]

It is my clinical experience that *Saccharomyces boulardii*, in particular, is a very good probiotic for prevention and treatment of TD. And there is good evidence to support probiotic approaches, especially *S. boulardii*, in the treatment of those who develop irritable bowel syndrome-like symptoms as a complication of TD.[4]

I would highly recommend probiotic approaches as safe and efficacious for the treatment and prevention of TD.

2) Loperamide being recommended for diarrhoea:
A previous edition of the Antibiotic section of Therapeutics Guidelines[5] advised not to use antidiarrhoeal preparations, including loperamide, because they delay excretion of the pathogenic organism. I note that the current eTG suggests a limited role for loperamide for short-term control of diarrhoea and never for use in young children as Dr Leder mentioned.[5] Although it is inconvenient to have diarrhoea (most of us have been there!) are we at risk of prolonging TD by treating with antidiarrhoeals? Or is this risk eliminated with the concurrent use of an antibiotic along with the antidiarrhoeal?
I welcome Dr Leder's feedback.

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Reply

I thank Dr Pennington for his interest and comments on this review. As regards the efficacy of probiotics, they colonise the gastrointestinal tract (GIT) and, theoretically, may prevent pathogenic organisms from infecting the bowel. I stated that 'Several probiotic agents have been studied for treatment and prevention of TD…[and] their effectiveness for TD prevention has been limited….'. On reflection, I could have more carefully differentiated between the effect of probiotics for TD treatment and TD prevention, and perhaps should have referred to their benefit as being controversial rather than limited.

For TD prevention, as Dr Pennington stated, a meta-analysis by McFarland did show benefit.[1] However, as per a subsequent review by Pham et al,[2] 'The results from trials studying the role of probiotics in preventing TD are inconsistent', and a more recent placebo-controlled trial has shown no beneficial prophylactic effect.[3] Thus, recent expert guidelines conclude that 'The use of probiotics, such as *Lactobacillus* GG and *Saccharomyces boulardii*, has been studied in the prevention of TD in small numbers of people. Results are inconclusive…'.[4] On this basis, I do not recommend probiotics to travellers, but acknowledge there are different practices and opinions.

The Cochrane review that Dr Pennington cited[5] relates to the treatment of diarrhoea. Although a benefit of probiotics was reported, the generalisability and applicability of these data for TD, rather than for all-cause diarrhoea, has not been established. Specifically, this review pointed out that there is better evidence for efficacy of probiotics for viral diarrhoea, but that 'Few studies reported outcomes for participants with bacterial diarrhoea and … more research is needed to assess probiotics in bacterial diarrhoea'. Given that TD is most commonly caused by bacteria, in the specific context of TD treatment, I believe the place of probiotics remains controversial and ill-defined. Moreover, as acknowledged in the Cochrane paper, 'more research is needed to identify exactly which probiotics should be used for which groups of people, and also to assess the cost effectiveness of this treatment'.

As regards the potential risks of using loperamide and delaying excretion of pathogens, many studies have shown the safety of loperamide used in combination with antibiotics (refer to refs in original article). However, the issue of when and for whom antibiotics should be recommended is likely to be a source of considerable further controversy and change. A research paper published since I wrote my review found that travellers who took antibiotics for TD were more likely to be found to be colonised with multi-resistant GIT bacteria on return (OR 4.2, 95% Cis 2.3–7.7), leading the authors to recommend restriction of antimicrobial use for severe TD while travelling.[6] An accompanying editorial[7] concludes that current practices vary and that we should 'stay tuned' as to the impact of emerging

data on advice given by travel medicine practitioners. My practice of recommending symptomatic relief with loperamide for mild diarrhoea, plus addition of an antibiotic for moderate or severe diarrhea, based on the evidence outlined in the original article, will not (yet!) change.

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Food allergies

I thank Rueter et al[1] for their interesting article on IgE-mediated food allergy (*AFP* October 2014). It is important to mention in this context that in recent years, more and more cases of red-meat-induced allergy and of sensitisation to carbohydrate epitope galactose-alpha-1,3-galactose (α-Gal) have been reported to have occurred worldwide, even in children.[2,3] Characteristically, this sensitisation occurs with a delay of 3–6 hours after the consumption of mammalian meat products (eg beef, pork or lamb). It manifests as urticaria, angioedema, itching and gastrointestinal disorders, or even as severe systemic anaphylactic reactions.[2–4] Because the symptoms occur with a delay after the consumption of meat, there might be a high number of unreported cases of individuals with IgE antibodies specific for alpha-gal-positive meat allergies among children, for whom physicians have been unable to make a clear diagnosis as to the cause of severe allergic reactions. In my opinion, practising physicians should not underestimate the significance of red meat allergy, particularly against the backdrop of increasing meat consumption in the USA, Europe, China and Australia.

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Reply

Thank you for the response to our article. We agree that apart from immediate-onset anaphylaxis (5–30 minutes after ingestion or injection of an offending agent) physicians need to be aware of delayed-onset anaphylaxis, which occurs 3–6 hours after ingestion of mammalian food products. Urticaria, angioedema or delayed anaphylaxis to mammalian meat products were first described in the adult population in 2009,[1] but subsequently also noted in older children.[2] A subgroup of these patients will also be allergic to mammalian milks and animal-derived gelatin.[3]

The target allergen associated with these reactions is an oligosaccharide known as galactose-α-1, 3-galactose (α-Gal). IgE antibodies specific for α-Gal bind to a wide range of mammalian proteins and induce the syndrome of 'delayed anaphylaxis to mammalian meat'.[1] α-Gal is also present in the gastrointestinal tract of ticks, and possibly in their saliva, as there is evidence that tick bites are the primary cause of this antibody response.[4,5]

Delayed anaphylaxis to red meat can be masked as idiopathic anaphylaxis (where the triggering antigen is unknown). It would be advisable to retrospectively evaluate children and adults diagnosed with idiopathic anaphylaxis for a delayed reaction to mammalian meat and tick bites, as establishing the aetiology of anaphylaxis is pivotal for long-term risk management.[5] In this context it is important to note that patients with IgE antibodies to α-Gal may not experience adverse reactions after every ingestion of mammalian meat.[2] The nuances of the delayed reactions seem to reflect that dose, temporal proximity to tick bites and meat composition are important in influencing the severity of allergic reactions.

Blood testing for specific IgE antibodies to mammalian meat and α-Gal will assist in confirming the diagnosis. Skin allergy testing to commercially available mammalian meats is much less reliable.[5]

Management of cases with delayed anaphylaxis to red meat consists of education combined with avoidance of red meat ingestion and further tick bites.

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Letters to the Editor

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