Journal of Travel Medicine

International Society of Travel Medicine
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Journal of Travel Medicine, 2019, 1–2
doi: 10.1093/jtm/taz014
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Rifamycin SV-MMX® as the recommended self-treatment for moderate to severe travellers' diarrhoea: reply

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Submitted 20 February 2019; Revised 21 February 2019; Editorial decision 21 February 2019; Accepted 18 March 2019

The questions raised by Drs Ericsson, Connor and Riddle on our study on the efficacy and safety of Rifamycin SV-MMX® for treatment of travellers' diarrhoea[1] (TD) allow us to more clearly state our position on this novel agent in the self-treatment algorithm of incapacitating TD. The three experts suggest we consider this treatment in face of the occurrence of invasive pathogens that can cause dysentery among travellers potentially armed with ineffective treatment.

There are two points that we believe important in considering this fact. The overwhelming majority of TD patients experience non-dysenteric TD; only 2–7% in various parts of the world are affected by dysenteric TD with fever and/or grossly blood admixed with the stools.[2] Also, afebrile, non-dysenteric TD caused by potentially invasive pathogens is rare. In the two pivotal studies with Rifamycin SV-MMX®, we found potentially invasive bacterial pathogens only in 15 (5.4%) of 264[3] and 0 (0%) of 30[1] patients recruited in Latin America and 84 (10.4%) of 805 in India.[1] That means that, in most of the destinations, over 90% of TD patients experience non-dysenteric TD by non-invasive bacteria and thus can be safely treated with a non-absorbed antibiotic as recommended if TD is incapacitating. Even for the remaining 10%, Rifamycin SV-MMX® appeared to be better than placebo, but statistical significance was not reached due to low numbers.[3] In any case, TD patients in a low-income country would never know in time whether or not they are infected by invasive pathogens. Additionally, bacterial TD is invariably a self-limited disease, allowing the more ill or persistently ill traveller to seek medical care when convenient, often on returning home.

Ericsson and colleagues claimed that the median duration of patients with potentially invasive bacteria in the Rifamycin SV-MMX® arm of the current study[1] was similar to the placebo arm of the pivotal rifaximin study.[4] Independent of the fact—as Ericsson *et al.* correctly state—that comparisons across studies conducted in different parts of the world are hazardous, and for that reason control arms are included in studies, this observation is incorrect as different definitions of the time to the last unformed stool (TLUS) were used in these two studies. If, in contrast, we compare the similarly defined clinical cure/wellness rate, patients with potentially invasive bacteria treated with Rifamycin SV-MMX® had a rate of 69.7% (per-protocol population; data on file), which was higher than the clinical wellness rate of 55.6% in placebo-treated patients with potentially invasive bacteria in the rifaximin study.[4]

To expect that travellers would carry with them two antibiotics against usually self-limited TD is not practical because of the cost and complex instructions on use. To those wishing to carry a travel kit with an agent against TD, we would recommend including only a single non-absorbable antibiotic. As described, this option is effective for most cases of TD and is associated with less-adverse reactions as compared to systemic antimicrobials. Resistance to azithromycin now exceeds 25% in *Escherichia coli* isolates from TD patients from Asia and Africa, while fluoroquinolones have become obsolete.[5] Rifamycin SV-MMX® when used without loperamide is not associated with an increase in extended-spectrum β-lactamase-producing *E. coli* (ESBL-PE) carriage.[1] Data for rifaximin without loperamide on ESBL-PE acquisition are lacking, but together with loperamide, rifaximin was associated with increased ESBL-PE colonization rates.[6] In this context, further placebo-controlled studies with Rifamycin SV-MMX® as a single-dose regimen together with loperamide and also of rifaximin used without loperamide would be of high interest. Prescribing a topical antibiotic that

does not increase ESBL-PE colonization is advantageous, not only for the individual but also from a public health perspective. Using systemic antibiotics broadly will contribute to resistance, making infections more difficult to treat.

Patients with invasive TD should seek medical advice if the symptoms are severe or persistent. They could be instructed to seek therapy with a systemic antibiotic such as azithromycin at a local pharmacy in the many countries where this agent is available over the counter. Only travellers to remote areas without access to any medical facility should consider additionally carrying azithromycin as second line therapy for rescue therapy.

In conclusion, no single drug is perfect against TD. We rate the advantages of non-absorbed antibiotics—reduced risk of adverse events, improvement in disease in most patients with illness, reduced risk of acquisition of multiple drug-resistant organisms (so far demonstrated only for Rifamycin SV-MMX®) and, lastly, protection of systemic antibiotics against resistance—greater than the disadvantages such as personal harm and public health impact, that a small minority of TD patients with invasive illness would not be initially treated by a systemic antibiotic as the first-line drug from a travel kit for self-treatment. While our recommendation does not fit with the ISTM consensus statement published in 2017 on the treatment of incapacitating TD,[7] we feel that these recommendations need to be updated intermittently as new data become available.

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