Treatment of Shiga-Like Toxin–Producing Escherichia coli Infection

TO THE EDITOR—The findings of Bennish et al. [1], with regard to a reduction in the frequency of hemolytic uremic syndrome (HUS) among patients who received appropriate antibiotics for Shigella dysenteriae infection, should resound interest in designing a prospective antibiotic treatment trial for enterohemorrhagic Escherichia coli (EHEC) infection. As the authors detail, Shiga toxin is analogous to one of the common Shiga-like toxins, which are produced by EHEC. Furthermore, there is considerable phylogenetic similarity between E. coli and Shigella species. Both of these factors enhance the theoretical potential that EHEC infections could be benefited by similar treatments, including antimicrobial chemotherapy.

As I have previously suggested [2], the choice of antibiotic is critical, because previous studies have shown that, despite in vitro susceptibility, only certain antibiotics are effective for shigellosis [3]. Wong et al. [4] proposed that antibiotics may be a risk factor for progression to HUS during EHEC infection, but the stratification and categorization of antibiotic use would not be consistent with shigellosis treatment trials.

A recent meta-analysis from Safdar et al. [5] did not find an increased risk of HUS in EHEC infection. Data from Bell et al. [6] and Proulx et al. [7] also provide similar findings. The latter studies complement those by my colleagues and me [8], in which the safety of certain antibiotics for treatment of E. coli O157:H7 infection was proposed. In other research, we found a possible protective effect of particular antibiotics [9, 10]. Although these studies are not definitive with regard to safety and protection, they, along with the supportive findings of Bennish et al. [1], provide plenty of fuel for hypothesis testing. It is justifiable to propose that an advance in treatment is possible.

Caution in the use of antimicrobial chemotherapy is justified, but such caution should not jeopardize the execution of prospective, randomized treatment trials. A choice of ampicillin for the therapeutic trial would be preferable, given the theoretical risk of complicating an evolving nephropathy with a relatively insoluble sulphonamide combination. The treatment group would ideally include children of young age who are at greater risk for progression to HUS and children who are seen early in the course of the illness. The randomized design would necessarily include a preconceived number of patients to achieve sufficient power, but the randomized code and the interim results could be available to an independent oversight group, which would ensure that the study be terminated if preliminary data showed an obvious trend towards adverse effects of antibiotic treatment. The time has come to move forward.

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Enterobacterial Repetitive Intergenic Consensus–Polymerase Chain Reaction for Typing of Uropathogenic Escherichia coli Is Not What It Seems

To the editor—France et al. [1] report studies of clonal relationships between antimicrobial-resistant uropathogenic Escherichia coli (UPEC) using enterobacterial repetitive intergenic consensus (ERIC)–PCR and other typing techniques. Previously, Manges et al. [2, 3] reported a related group (clonal group A) of E. coli associated with urinary tract infection. In subsequent correspondence, there was discussion of the limited reproducibility of ERIC-PCR [4–6]. We also have studied ERIC-PCR as part of an investigation of relationships between UPEC in our region. We included E. coli ATCC 25922 and E. coli K12 as controls in each PCR run. PCR products were obtained from K12 and ATCC 25922; however, there was a great deal of variability with respect to the patterns obtained in 3 consecutive PCR runs performed by the same operator with the same lot of template DNA, reagents, and thermal cycler. This experience is consistent with those reported in recent correspondence and by Meacham et al. [4–7]. This prompted us to review the basis of ERIC-PCR typing.

ERIC sequences are highly conserved 126-base pair (bp) noncoding regions that are repeated multiple times through the bacterial genome. The location of ERIC sequences varies from strain to strain [7, 8]. In 1991, Versalovic et al. [9] reported ERIC-PCR typing. This method is based on the expectation that complementary oligonucleotides will anneal to ERIC sequences and that the DNA between the ERIC sequences may be amplified, provided that the interval between ERIC sequences is <5 kilobases. Because there are multiple ERIC sequences, there is potential for amplification of multiple PCR products. Variation in the number and location of ERIC sequences between unrelated strains of E. coli is expected to result in differences between strains in the number and size of PCR products. Differences in the number and size of PCR products result in differences in banding patterns when the products are separated by electrophoresis. The Web site of the Pasteur Institute [10] indicates that there are 21 ERIC sequences in the sequenced E. coli K12 genome, which we used as a control. It is apparent from this sequence, which was not available in 1991, that the smallest interval between 2 ERIC sequences in E. coli K12 is 42,404 bp. This interval is far beyond the range of amplification of conventional PCR and much greater than the size of products identified on ERIC-PCR gels [1]. We believe that the theoretical basis for ERIC-PCR, which has become important in the investigation of the clonal relationships between UPEC, is flawed. Given the interval between ERIC sequences, at best, one can anticipate that one of the primers related to each product generated in an ERIC-PCR run anneals to an ERIC sequence, with another copy of the primer annealing to a partial sequence match under low stringency (50°C) annealing conditions. ERIC-PCR may be considered to be a variant of random amplification of polymorphic DNA–PCR, which also lacks reproducibility. The flawed basis of ERIC-PCR explains the lack of reproducibility of the technique and adds emphasis to calls for caution in the interpretation of results based on this method.

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