EHEC infection and antibiotic therapy

The current outbreak of gastrointestinal infection due to shigatoxin-producing *Escherichia coli* (STEC, also called enterohemorrhagic *E. coli*, EHEC) in Germany is associated with an unusually high attack rate in female adults and a relatively high rate of hemolytic uremic syndrome (HUS) as a severe complication (~1 HUS case for 3-4 EHEC cases). The causative organism has been characterized as *E. coli* O104:H4, stx2-positive, eae-negative, iha-positive, ESBL-positive, but gentamicin and fluoroquinolone-susceptible, and combines several virulence traits in an unusual manner. The source of the outbreak and the origin of the strain remain unclear. Eating (fresh) tomatoes, cucumbers and salad has been associated with disease in a case-control study as published by German authorities. More information is available at www.rki.de and www.ehec.org.

Antibiotic therapy has been discouraged after earlier experience indicating a danger of aggravating the disease due to induced or enhanced liberation of the verotoxin which is pathophysiologically critical for the disease and its complications. The relevance of this recommendation for clinical management in the present outbreak situation has been questioned. The German Society for Infectious Diseases (DGI) - in association with other professional societies in the country - has reviewed and evaluated the available information on the issue and has drafted this position paper on antibiotic therapy in current outbreak EHEC patients.

Background information

Previous clinical studies did not demonstrate beneficial effects of antibiotic therapy on the outcome of EHEC infection. In several retrospective studies, often with small numbers of evaluable patients, antibiotic therapy was rather linked to a higher rate of HUS, a prolonged period of symptomatic disease and prolonged EHEC shedding. Among the antimicrobial agents prescribed in those studies were typically cotrimoxazole and fluoroquinolones. Other studies were unable to demonstrate such an association. Many previous observational studies included only pediatric patients. Some information on the association between antibiotic use and increased HUS risk is derived from outbreaks of *Shigella* infection.

In vitro and animal studies have repeatedly demonstrated a possible induction of toxin production or toxin release from EHEC after exposure to antimicrobial agents. The heterogeneity of the models, methods and drugs used in these studies, and strain dependence make it difficult to compare different antibiotics or antibiotic drug classes, to assess drug-specific differential effects and to draw conclusions about the clinical relevance of the findings. However, relatively consistent results have been obtained in studies with
fluoroquinolones, cotrimoxazole and also with aminoglycosides. Exposure to these antibiotics obviously can lead to enhanced shigatoxin production or release. Observations with ß-lactams, macrolides, clindamycin and fosfomycin appear to be less consistent. The limited information available suggests that ampicillin might be more unfavourable than cephalosporins which, in turn, might be more unfavourable than carbapenems. Macrolides and clindamycin may, in fact, lower toxin production in EHEC cells. No induction of toxin production or release has been observed with rifampicin, rifaximin and tetracyclines. Tigecycline has not been evaluated in this respect. Given its chemical structure (derived from minocycline) and mode of action, it is likely that effects on EHEC regarding shigatoxin release will be similar to those observed with tetracyclines.

In animal studies, both macrolides (compared to fluoroquinolones) and rifampicin (compared to untreated controls) have been associated with better survival and/or less adverse effects of EHEC infection while ciprofloxacin treatment in animals (compared to untreated controls and azithromycin) decreased survival. Fluoroquinolones have shown beneficial effects in an experimental model only when administered very early after challenge. Fluoroquinolones – unlike most of the agents discussed above – have been associated with phage activation (potentially resulting in enhanced intraintestinal transfer of Stx2 prophage from one *E. coli* to another).

The current EHEC O104:H4 outbreak strain HUSEC41 is an ESBL producer and must be considered resistant to penicillins and cephalosporins licensed and currently used in this country. Further information on antimicrobial susceptibility of this strain will be available at the homepage of the Robert-Koch-Institute (www.rki.de) or at www.ehec.org.

**Recommendations**

In view of the above preclinical and clinical studies and observations the panel recommends that fluoroquinolones and cotrimoxazole, but also aminoglycosides and fosfomycin should not be used in current EHEC outbreak patients. The potential of untoward effects and a higher risk to develop complications outweighs the chances of a potentially rapid eradication of the pathogen from the intestinal tract, although the available evidence is somehow more limited on aminoglycosides and fosfomycin. There is no comparable evidence available to discourage the use of newer macrolides, clindamycin, rifampin and rifaximin if needed. Similarly, carbapenems so far have not been associated with untoward effects in EHEC infection.

Antibiotic therapy may be indicated in patients infected with the current EHEC outbreak strain for a number of reasons. Of note, previous observations on potentially untoward effects of antibiotic therapy were made in patients who had been pretreated with antibiotics (indication gastroenteritis or even for other reasons prior to diarrhea onset) and who were then evaluated for complications following antibiotic therapy. There are, in contrast, no reports about untoward effects of antibiotic therapy in patients who already have developed EHEC-associated HUS or other severe complications although such effects cannot be totally excluded in patients persistently carrying the EHEC strain.

The panel currently recommends that

- if according to clinical judgement antibiotic therapy is needed in an EHEC or EHEC/HUS patient (for example if one suspects invasive disease due to the EHEC strain itself or due
to a superinfecting microorganism) a carbapenem should be used and be the preferred choice over other drugs/drug classes

- if needed for other reasons (for example for eradication of nasopharyngeal meningococcal colonisation because of planned treatment with eculizumab) treatment with newer macrolides and rifampicin is also considered safe and should not be withheld for reasons of fear of possible aggravation of EHEC/HUS disease; it remains highly controversial and there is insufficient evidence to conclude that these drugs incl. clindamycin should be used in EHEC infection as anti-virulence drugs

- in patients with persistent EHEC colonization, severe disease and clinical progression but without indication for systemic antibiotic therapy rifaximine may be a useful and safe option for eradication of EHEC from the intestinal tract while the use of oral (non-absorbable) aminoglycosides (for example paromomycin) cannot be recommended due to conflicting data from in vitro studies regarding shigatoxin production or release. Rifaximine is licensed in Germany and other countries for the treatment of traveller’s diarrhea caused by different enteropathogenic E. coli and other bacteria. It has also been used with success for the treatment of Clostridium difficile infection and in patients with hepatic encephalopathy.

This position paper was drafted (originally June 1) and consented by an expert panel of the German Society for Infectious Diseases (DGI, Kern, Fätkenheuer, Salzberger, Suttorp, Ruf, Brodt) in cooperation with delegates of the German Society of Hygiene and Microbiology (DGHM, Peters, Suerbaum), the German Society of Nephrology (DGfN, Brunkhorst) and the Robert-Koch-Institute (RKI, Eckmanns, Krause, Mielke). Panelists at the time of the translation into English included Béatrice Grabein as delegate of the Paul-Ehrlich-Society for Chemotherapy (PEG).

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References

In vitro studies:


Animal studies


Other studies incl. clinical observations and reviews


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