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Review Article

Antibiotic therapy in Shiga toxin producing Escherichia coli infection and colonization

Abstract

The post diarrheal hemolytic uremic syndrome (HUS) is a major complication of enteric infections with Shiga toxin producing *E. coli* (STEC). According to the present recommendations, antibiotic therapy of acute bloody diarrhea caused by STEC is generally discouraged. These recommendations are based on historically conflicting results describing the potential induction of HUS by antibiotic treatment during the early phase of infection with enterohemorrhagic *E. coli* O157 whereas no guidelines are available for the use of antibiotics in cases of already fully established HUS or in asymptomatic long term STEC carriers. In 2011, a large outbreak of hemorrhagic colitis complicated by HUS occurred in northern Germany caused by a STEC strain of serotype O104:H4 harbouring both a phage encoding Stx 2 as well as a plasmid mediated enteroaggregative phenotype. The majority of infections were observed in adults, complicated by the highest number of HUS cases ever encountered. Due to different newly introduced therapeutic strategies (e.g. complement blockade) antibiotic therapy was used in many patients once HUS was established. The outbreak therefore provided important new insights for the understanding of antibiotic therapy of STEC associated HUS in adults and for decolonization of long term STEC carriers. This review highlights new aspects concerning use of antibiotics in STEC infection and colonization.

Keywords: Shiga toxin producing E. coli, enterohemorrhagic E. coli, haemolytic uremic syndrome, O104:H4 outbreak, STEC decolonization

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Introduction

The hemolytic uremic syndrome (HUS) was first described by Gasser et al. in 1955 with the clinical hallmarks of acquired hemolytic anaemia, acute renal failure, hemorrhagic diathesis and cerebral symptoms [1]. Nowadays, HUS is classified as typical or post-diarrheal (D+) HUS versus atypical HUS not preceded by infectious diarrhea (D-) [2]. Development of D+ HUS is based on diarrheagenic bacteria expressing Shiga toxins (Stx) including *Shigella dysenteria* type 1 and *Escherichia coli* (STEC). STEC infections associated with D+ HUS were first described as Vero toxin producing *E. coli* (VTEC) about 30 years ago [3], [4]. STEC strains can express Stx 1 and/or 2, also known as Vero toxins or Verocytotoxins, which are encoded by phages [4], [5]. The toxin is believed to be responsible for the vascular damage (hemorrhagic colitis) and for systemic effects as seen in HUS. For both Stx 1 and Stx 2 several allelic variants are described, of which Stx 2 and 2c are more frequently associated with HUS development than others [6], [7]. The presence of the *eae* gene which is characteristic for enteropathogenic *E. coli*, grants adherence to the intestinal mucosa and defines the "classical" enterohemorrhagic *E. coli* (EHEC) subset within the STEC family. STEC strains lacking *eae* have traditionally been regarded as less virulent, but were also documented as causative agents of STEC disease including the recent German outbreak [8], [9]. *E. coli* can be serotyped by their O an H antigens. In the vast majority of STEC-related D+ HUS the serotype O157:H7 was reported [10]. However, in some parts of the world non-O157 serotypes like O26 and O111 caused up to half of all D+ HUS cases [11], [12]. Ruminant animals (especially cattle) are considered reservoirs of STEC. Transmission usually occurs via contaminated food or water.

STEC are commonly viewed as rare pathogens that cause severe disease predominantly in children. Before 2011, about 1,000 infections per year and less than 100 cases of HUS were registered in Germany in a nationwide surveillance [13]. According to the guidelines for STEC infections, antibiotic therapy of acute bloody diarrhea is generally discouraged due to its assumed potential to induce or promote D+ HUS in infections caused by enterohemorrhagic *E. coli* O157. In 2011, a large outbreak occurred in northern Germany caused by a STEC strain of serotype O104:H4 with the highest number of HUS cases ever encountered. A major issue discussed in the therapy of STEC infections deals with the question of whether or not to discourage the use of antibiotics. This review will discuss conflicting data on antibiotic therapy in STEC infection from both *in vitro* and *in vivo* studies. New concepts,

especially concerning decolonization of patients in the post-diarrheal phase, will be highlighted.

Interaction of antibiotics and STEC in vitro

It is widely accepted that Stx production is boosted *in vitro* by subinhibitory concentrations of specific antibiotics with a possible impact on HUS pathogenesis. Since the early nineties, this topic has been investigated extensively. Results are partially conflicting and difficult to compare due to a variety of STEC strains investigated. Additionally, various antibiotics in inhibitory and subinhibitory concentrations as well as multiple methods for detection of phage induction and/or modification of Stx expression and the release of active toxin were used [14], [15], [16], [17], [18].

Due to these discrepancies in study design, solid data is mainly available for EHEC O157 and for two classes of antibiotics, the fluoroquinolones and trimethoprim-sulfamethoxazol (TMP/SMZ). Both substances have repeatedly been shown to induce Stx production *in vitro*, especially when applied in subinhibitory concentrations [15], [17], [19], [20]. This is highly plausible, as both antibiotics, targeting DNA synthesis, induce the bacterial SOS stress response to DNA damage which is linked to an increase in phage production and toxin release [17], [18].

For other antibiotics like makrolides, fosfomycin, clindamycin, cephalosporins and carbapenems results have been conflicting, showing either an increase or a decrease in Stx production or even no change at all [17], [20], [21]. Apart from variations in study design, this might be attributed to a strain dependent response to antibiotics [15], [16], [22]. Pedersen et al. showed that makrolides (azithromycin, telithromycin) at minimum inhibitory concentrations (MIC) increased Stx release from Stx-1 producing strains but decreased toxin release in STEC harboring Stx-2 variants with the exception of serotype O157 [16]. However, Stx induction from pure cultures may differ from Stx production in the complex intestinal environment [17]. For the recent outbreak strain STEC O104:H4, Bielaszewska et al. [23] confirmed that azithromycin did not induce Stx expression *in vitro*. Comparing subinhibitory concentrations of various antibiotics on the induction of Stx production of STEC O104:H4 they found that ciprofloxacin increased, while meropenem, rifaximin, tigecycline and azithromycin did not affect Stx production [23]. In the outbreak situation, early evaluation of these interactions was helpful to precisely determine the risk of antibiotic treatment.

Antibiotic therapy in acute STEC diarrhea and haemolytic uremic syndrome

Looking back on previous STEC outbreaks or sporadic infections, the impact of antibiotic treatment on the course of disease yielded inconsistent results. The vast majority of these reports exclusively dealt with EHEC O157 infections [24], but limited evidence is present in EHEC/STEC infections caused by other serotypes. The following section of this review comprises data discrediting the use of antibiotics, showing neither positive nor negative effects as well as potential benefits at least in the analyses of subgroups.

In 1990, a high rate of HUS was observed in patients receiving TMP/SMZ or sulfasalazine in a case control study of O157 infections [25]. All of these patients had received antibiotic treatment during the first 72 h of diarrheal illness. Consistently, in a prospective cohort study including 71 children aged less than 10 years, an increased risk for HUS was confirmed for TMP/SMZ administration during the first three days of diarrheal illness. Here β-lactams were identified as a second class of antibiotics increasing the likelihood of progression to HUS [26]. In a recent large multicentre trial analysing risk factors for the development of HUS in children infected by EHEC O157:H7 [27], antibiotic exposure during the first 7 days after onset of diarrhea was associated with increased risk of HUS development (OR 3.62; 95% CI, 1.23–10.6; p=0.02) in the overall analysis. Subgroup analysis of particular antibiotic substances revealed a significantly increased risk only for TMP-SMZ and metronidazol, whereas no significant differences were observed for β-lactams and azithromycin [27].

In a large case control study of O157 infections between 1996 and 2002 antibiotic treatment was not associated with HUS development in general [28]. However, subgroup analysis again revealed an increased risk for HUS if bactericidal antibiotic therapy was administered in the early phase of disease. The case control study presented by Slutsker et al. did not find an association between antibiotic treatment and progression to HUS [29]. Subgroup analysis in this study revealed that patients <13 years old who developed HUS were more likely to have received any antimicrobial agent within the first three days after onset [29]. In a retrospective analysis of a large O157 outbreak taking place in Scotland in 1996 [30], the administration of ciprofloxacin in the early stage of EHEC O157 hemorrhagic colitis was associated with a trend towards higher incidence of HUS, without reaching statistical significance. Administration of antibiotics during the four weeks preceding the onset of O157 disease, however, significantly increased the risk of developing HUS. This might be explained by residual subinhibitory intestinal concentrations after the end of antibiotic treatment. Alternatively, alterations of the post-antibiotic gut flora might predispose to D+ HUS. This coincides with reports from 1987 showing that antibiotic treatment prior

to infection with *E. coli* O157 was associated with the risk of secondary transmission during an outbreak in a nursing home [31]. During this outbreak antibiotic treatment was also associated with an increased case fatality rate. However, this finding was interpreted cautiously by the authors, due to selection bias.

In summary, the afore mentioned studies may lead to the conclusion, that the first few days of acute hemorrhagic colitis might constitute a vulnerable period for an increased risk of HUS induction due to antibiotic treatment. Moreover, pre-diarrheal antibiotic exposure might increase the risk of HUS.

These findings are, however, in some contrast to a retrospective analysis of 278 children infected with EHEC O157 during an outbreak in Washington State in 1993. Here, no significant difference (OR 1.3; 95% CI, 0.6–2.6; p=0.56) in HUS development was observed between those children receiving antibiotics (16%, n=50) and those patients where antibiotics were withheld (12.8%, n=278), respectively [32]. In a subanalysis the administration of TMP-SMZ was accompanied with a slightly increased rate of HUS development (19.4%) still not attaining statistical significance (OR 1.5; 95% CI, 0.7–3.3; p=0.32). Moreover, TMP-SMZ treatment had no significant effect on the duration of EHEC shedding. Interestingly, in contrast to reports of TMP/SMZ as a risk factor for HUS, a prospective trial with TMP/SMZ in 47 children during O157:H7 enteritis [33] reported a lower incidence of HUS in the antibiotic group (9.1%) compared to untreated children (16.0%) without however statistical significance (p=0.67). In the analysis of 238 hospitalized patients with confirmed EHEC O157 infections in an endemic situation in New York State between 1998 and 1999 no significant association between antibiotic therapy and HUS development was observed [34].

Only few studies described a potential benefit for patients treated with antibiotics if given at the very early stage of disease. In 1999, Ikeda et al. reported a reduced risk of HUS development in patients receiving fosfomycin within the first two days of bloody diarrhea compared to patients not treated with fosfomycin at this very early stage [35]. However, the control group mainly consisted of patients treated with fosfomycin at a later time or with other antibiotics, but did not include a sufficient number of patients lacking any antibiotic therapy. In contrast to this study, Shiomi et al. reported reduced HUS development by early administration of oral fluoroquinolones compared to intravenously administered fosfomycin or oral fosfomycin in combination with intravenous cefotaxime [36]. Cimolai et al. reported a lower incidence of HUS in those patients treated with antibiotics, which however, could not be confirmed in the subsequent multivariate analysis [37]. In this study, the classes of antibiotics administered were not stated in detail.

In conclusion, some reports were able to demonstrate an increased risk for progression to HUS related to antibiotic exposure during diarrheal illness caused by EHEC O157. However, most studies reported neither beneficial nor adverse effects of antibiotic treatment in general and only few studies reported possible beneficial outcomes in specific subgroups of patients.

Based on these inconsistent reports in previous literature, the use of antibiotics was strongly discouraged during the 2011 German outbreak unless secondary complications urged for antibiotic treatment. Clinicians were confronted with a high number of adult patients with HUS-related severe acute kidney injury (high levels of blood urea nitrogen and serum creatinine), hemolysis and neurological complications [38], [39]. Standardized guidelines for causative treatment or randomized clinical trials approving any therapeutic concept to be beneficial beyond best supportive therapy were missing [40]. Therefore, therapeutic strategies were proposed *ad hoc* [41] based on theoretical considerations and preceding observations, but without any proof for the effectiveness of such “best guess” concepts. Moreover, these *ad hoc* strategies were continuously adjusted according to new observations made during the outbreak. Therefore, different medical centres used varying therapeutic regimens [42].

Despite the *in vitro* induction of Stx expression by quinolones and betalactams, pre-emptive therapy of STEC-HUS patients with a combination therapy of meropenem and ciprofloxacin in one medical centre in Northern Germany resulted in a statistically significant reduction of death, seizures and STEC shedding [42]. Results of previous studies analysing the influence of antimicrobial treatment on the clinical outcome of patients suffering from already fully established HUS were inconsistent. Martin et al. observed in a retrospective study patients with typical (n=101) and atypical (n=16) HUS that antimicrobial treatment before progression to HUS was associated with a mild clinical course. Only 3.0% of patients with severe disease received antibiotics compared with 22.6% of treated patients (p=0.01) displaying mild disease [43]. In a large prospective surveillance study in 395 patients suffering from D+ HUS, no differences were observed in the clinical outcome for patients (n=71) who had received antibiotics (β-lactams, metronidazol or ciprofloxacin) prior to admission to the hospital [44].

Antibiotic therapy in long term colonized carriers

By the end of May 2011 rapid clinical improvement under therapy with the anti-C5a antibody eculizumab was reported in three children suffering from STEC-HUS [45]. From this point on, patients of the German outbreak were therefore treated with eculizumab off-label. As eculizumab disrupts the complement cascade and thereby increases the risk for meningococcal meningitis [46], antibiotic meningitis prophylaxis was mandatory in non-vaccinated patients receiving this antibody-based therapy. For this purpose azithromycin was recommended in the *ad hoc* guidelines due to its documented *in vitro* inability to induce Stx production [41]. At the university hospital of Lübeck STEC-shedding was closely monitored. In patients

Table 1: Characteristics of HUS and non-HUS patients not treated with antibiotics [47]

	HUS (n=15)	non-HUS (n=28)	p-value*
age – yrs.	42.8 (±23.0)	51.3 (±21.1)	p=0.314
male sex	33.3%	35.7%	p=0.858
time investigated – days	43.7 (±8.4)	45.6 (±13.4)	p=0.828
time confirmed positive – days	32.4 (±19.2)	35.3 (±19.6)	p=0.980

* Mann-Whitney U test for age, time investigated and time confirmed positive; Chi-square test for gender

not treated with antibiotics, individuals who developed HUS were compared with individuals who had mild signs of infection (non-HUS; Table 1). The HUS and non-HUS groups were observed for similar periods. No significant differences in age or sex distributions were observed. The mean time of confirmed carriage was similar between the 2 groups (p=.98). This data indicates that the course of infection has no significant influence on STEC shedding. All patients who were treated with eculizumab and had received azithromycin as meningitis prophylaxis were rapidly decolonized from STEC O104:H4, while untreated patients displayed significantly longer STEC shedding [47]. In detail, among azithromycin-treated HUS patients, long-term STEC carriage (>28 days) was observed in 1 of 22 patients (4.5%; 95% CI, 0%–13.3%), compared with 35 of 43 patients with or without HUS (81.4%; 95% CI, 69.8%–93.0%) who were not treated with this antibiotic (p<0.001). All 22 patients receiving azithromycin had at least 3 STEC-negative stool specimens after the completion of their antibiotic meningitis prophylaxis, and no recurrence of STEC was observed in these patients. The shortening of STEC shedding by azithromycin treatment was also confirmed by a larger multicenter study [48].

In contrast to the most prevalent STEC strains, the O104:H4 outbreak strain had an enteroaggregative phenotype, which might mediate the high rate of long term carriage. Azithromycin is an approved therapy in diarrheal disease caused by enteroaggregative *E. coli* [49]. Therefore, as proof of principle, a three day course of oral azithromycin (500 mg/d) was offered at our hospital to long term carriers (>28 d) of STEC O104:H4 who had initially not been treated with antibiotics, but, though now asymptomatic, were restricted in their social or working life (e.g. ban from work). After the 3-day course all 15 long term carriers treated with azithromycin for STEC decolonization had consistently negative stool specimens without any deterioration of renal function or development of other HUS related symptoms [47]. Therefore, successful decolonization treatment was extended to more than 40 persons without any adverse effects (unpublished data) up to the present time. Such a decolonization regimen, however, must always be weighed cautiously against the risk of other potential, pathogen-independent adverse drug side effects. Moreover, it has to be taken into account, that all promising results concerning the use of antibiotics for the treatment of STEC during the German STEC O104:H4 outbreak were retrieved either from patients already suffering from HUS, or from clinically recovered, now asymptomatic long-term carriers with a shedding time of at least 28 days. Therefore, at present, no definite conclusions can be drawn for the use of antibiotics in acute STEC-related hemorrhagic diarrhea. Future research has to further elucidate the risk or benefit of specified antibiotic treatment in the prevention or induction of HUS in this and other STEC strains. To date, antibiotics should be handled cautiously in patients with acute bloody diarrhea caused by STEC until their benefit might be approved in controlled trials.

Future therapeutic strategies and needs for research

During the northern German outbreak of STEC O104:H4 in 2011, new aspects regarding the antibiotic therapy in STEC infections and HUS were investigated retrospectively raising new options for treatment in STEC disease and carriage. However, there are still many questions which must be answered in the future. From a clinical point of view, the previous dogma that antibiotics are absolutely contraindicated in STEC disease needs to be revised. In our opinion, the point of time during the course of STEC disease should be a key landmark for the decision of therapeutic interventions with antibiotics. The contraindication of antibiotic use during early STEC disease (diarrheal phase) should still be strictly followed as the interaction of antibiotics with the expression of the Shiga toxin is strain specific and each substance class might be able to increase the risk of severe disease. The development of diagnostic assays enabling rapid quantitative Shiga toxin detection in differential growth conditions should be developed to enforce a risk assessment for individual strains during the early phase of STEC diagnostics. In patients with already established HUS a strict contraindication of antibiotics in all STEC caused HUS cannot be perpetuated for all STEC strains. At least for STEC O104:H4 it was demonstrated that use of azithromycin did not worsen the outcome [47] and a combination antibiotic therapy including substances known to induce Shiga toxin expression might be even beneficial in patients with established HUS [42]. Further studies on the effect of antibiotic therapy in established D+HUS are necessary to evaluate the observations made during the outbreak for other individual STEC serotypes. In the case of long term STEC shedding the safe use of azithromycin as decolonization therapy was demonstrated for 15 patients carrying the O104:H4 outbreak strain [47]. Several additional O104:H4 carriers could be eradicated by azith-

romycin treatment with high efficiency (unpublished data), though the authors have little experience in decolonization of STEC strains other than STEC O104:H4. However, in individual cases azithromycin treatment resulted in sustainable eradication of non-O104:H4 STEC long term carriers (unpublished data). Therefore, we agree with Mody and Griffin [50], that azithromycin eradication therapy could be offered to long term carriers after detailed discussion of the possible risks of treatment in a case to case decision if patients are strongly affected in their social or economic living.

Notes

Competing interests

The authors declare that they have no competing interests.

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