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REVIEW

SWAB guidelines for antimicrobial therapy of acute infectious diarrhoea

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ABSTRACT

The Dutch Working Party on Antibiotic Policy (SWAB: Stichting Werkgroep Antibioticabeleid) develops evidence-based guidelines for the use of antibiotics in hospitalised adults. In this article we discuss the guideline on antibiotic treatment of acute infectious diarrhoea (AID). AID can be subdivided into community-acquired diarrhoea, traveller's diarrhoea and hospital-acquired (nosocomial) diarrhoea. For the first two categories, the need for antibiotic treatment is generally restricted to individuals with severe illness, dysentery and/or a predisposition to complications. Infection with *Campylobacter* species is the most common cause of bacterial AID in the Netherlands. In human *Campylobacter* isolates in the Netherlands, but also in other parts of the world, high rates of primary fluoroquinolone resistance are prevalent. If antibiotic treatment in community-acquired AID and AID in travellers on return to the Netherlands is indicated, it is therefore advised to use oral azithromycin for three days as empirical treatment. If intravenous treatment is necessary, the combination of ciprofloxacin and erythromycin for five to seven days may be used. As soon as the identity of the causative organism is known, antimicrobial treatment should be tailored accordingly.

KEYWORDS

Acute infectious diarrhoea, antimicrobial therapy, *Campylobacter*, guideline, resistance

INTRODUCTION

The Dutch Working Party on Antibiotic Policy (SWAB: Stichting Werkgroep Antibioticabeleid) initiates and coordinates activities aimed at optimisation of antibiotic policy in the Netherlands. Through the development of evidence-based guidelines for the use of antibiotics in hospitalised adults, it offers local antibiotic and formulary committees a tool for the development of their own local antibiotic policies.

We present here the SWAB guideline for acute infectious diarrhoea. Apart from meta-analyses and guidelines collected via the Cochrane Library (www.update-software.com/ebmg) and the National Guideline Clearinghouse (www.guideline.gov), relevant literature from the Embase and Medline electronic databases was used. In our guideline, a degree of evidential value was assigned to each of the recommendations according to the handbook of the Dutch Institute for Healthcare Improvement (CBO) (www.cbo.nl/product/richtlijnen/handleiding_ebro). The complete guideline is available at www.swab.nl. In this report, we will mainly focus on empirical treatment strategies. The most important conclusions from the literature review with their level of evidence are summarised in *table 1*. For a schematic overview of antimicrobial recommendations for individual causative agents we refer to *table 2*.

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Table 1. *Summary of conclusions of the literature review, with level of evidence*

Conclusion, reference	Level of evidence[#]
Campylobacter	
Early treatment with erythromycin for 5 days can reduce the duration of both symptoms and faecal excretion[58-61]	1
Early treatment with azithromycin 500 mg OD for 3 days appears to be effective as well[47]	3
Shiga toxin-producing E. coli (STEC)	
There is no favourable effect of antibiotics on symptoms of STEC-related AID[24]	3
A clear association between the use of antibiotics for STEC-related AID and HUS is absent[25]	1
STEC-related AID should not be treated with antibiotics	4
The use of antiperistaltics such as loperamide should be avoided[26,27]	3
Toxigenic Clostridium difficile	
Interruption of the offending antimicrobial is an important part of the treatment of CDAD, as it may lead to spontaneous recovery in 15-23% of cases[30,31]	3
Oral metronidazole (250 mg Q6h or 500 mg TD) and oral vancomycin (125 mg Q6h) for 10 days are equally effective for the treatment of CDAD[28,30,63]	1
Metronidazole is considered to be the treatment of choice, because it is effective and cheap and unlike vancomycin, its use is not associated with the emergence of 'vancomycin-resistant enterococci'	4
Treating silent *C. difficile* carriage is not useful[64]	3
Recurrent toxigenic Clostridium difficile infection	
A relapse is almost never the result of resistance to the initial drug, and a first relapse can be treated with the same antibiotic[31]	3
If relapses continue to occur after the first relapse, CDAD can be treated with a vancomycin taper or pulse regimen for 3-4 weeks[35,36]	3
Empirical treatment of community-acquired AID	
Antibiotic treatment with a fluoroquinolone has a favourable effect on duration and severity of symptoms if started within 5 days after the onset of disease[42-44]	1
Campylobacter spp. are the most frequently found causative agents of bacterial AID in the Netherlands. Resistance rates for fluoroquinolones amongst endemic *Campylobacter* strains are as high as 30.9% for *C. jejuni* and 39.2% for *C. coli*. For erythromycin, the resistance rates are 3.9 and 6.3%, respectively	NA
Azithromycin for 3-5 days is effective for the treatment of AID caused by *S. typhi*, and *Campylobacter* and *Shigella* spp.[47,48,50,51,65]	2
Empirical treatment of AID in travellers	
Antibiotics can limit the duration of symptoms[52]	1
A single dose of a fluoroquinolone and fluoroquinolone regimens with longer duration are equally effective[53,54,57,66]	1
A single dose of azithromycin (1000 mg) and a single dose of a fluoroquinolone appear to be equally effective[55]	3
The combination of an antibiotic and loperamide is more effective in terms of duration of symptoms than an antibiotic alone[54,56,57,67,68]	1
Loperamide is contraindicated in case of severe illness and dysentery	4

[#]Level of evidence according to the CBO manual: level 1: conclusion or recommendation is supported by at least two independent randomised studies of good quality or by a meta-analysis; level 2: supported by at least two randomised trials of moderate quality or insufficient size or another comparative study (not randomised, cohort studies, patient control studies); level 3: not supported by research of the above-mentioned levels; level 4: based on the opinion of members of the guideline committee. STEC = Shiga toxin-producing *E. coli*; HUS = haemolytic uraemic syndrome; CDAD = *Clostridium difficile*-associated disease; NA = not applicable, OD = once daily; TD = thrice daily; Q6h = every six hours.

DEFINING ACUTE INFECTIOUS DIARRHOEA

In the Netherlands, about 4.5 million cases of gastroenteritis are diagnosed every year, but a general practitioner is only consulted in one out of 20 cases.[1] An even smaller group of patients with diarrhoea will eventually be admitted to a hospital.[2] Children under the age of 5 are most frequently affected, but mortality is low.

A worldwide accepted definition of acute infectious inflammation of the gastrointestinal tract (acute infectious gastroenteritis) is not available and therefore the illness may be best characterised by its clinical symptoms such as diarrhoea, with or without blood and/or mucus, nausea, vomiting and fever, in combination with the detection of a viral, bacterial or parasitic pathogen. The World Health Organisation (WHO) defines diarrhoea as the evacuation of a minimum of three loose stools in 24 hours. Diarrhoea is qualified as 'acute' when symptoms are new and have not been present for more than 14 days. Dysentery is a diarrhoeal illness that involves the evacuation of bloody stools.

This guideline is restricted to acute infectious inflammation of the gastrointestinal tract manifesting primarily as diarrhoea, a condition that will be referred to as 'acute infectious diarrhoea' (AID). Therefore, *Helicobacter pylori* infections are not included. For the same reason, acute diarrhoea caused by ingestion of microbial toxins (food poisoning) and systemic infections accompanied by diarrhoea, such as legionellosis, listeriosis, viral hepatitis and other viral infections, fall outside the scope of this guideline. AID can be subdivided into community-acquired AID, AID in travellers and hospital-acquired (nosocomial) AID.

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Table 2. *Pathogen-directed therapy in acute infectious diarrhoea*

Pathogen	Antibiotic*	Comments
Bacteria		
Campylobacter spp.	1. Azithromycin, 500 mg OD orally, 3 days 2. Erythromycin, 500 mg BD iv, 5 days	No antibiotics unless high or persistent fever, dysentery or immunocompromised host
Salmonella spp. (non-typhi)	1. Ciprofloxacin, 500/400 mg BD orally/iv, 7 days 2. TMP-SMZ, 960 mg BD orally/iv, 7 days	No antibiotics unless high or persistent fever or dysentery. Immunocompromised host or prosthetic material in situ: treat for 14 days Long-term carrier state possible
Shigella spp.	1. Ciprofloxacin, 1000 mg single dose orally 2. Azithromycin, 250 mg OD orally, 5 days (first day 500 mg) 3. TMP-SMZ, 960 mg BD orally, 3 days	No antibiotics unless high or persistent fever or dysentery. Immunocompromised host: oral/iv ciprofloxacin 500/400 mg BD or TMP-SMZ 960 mg BD for 7-10 days
Yersinia spp.	1. TMP-SMZ, 960 mg BD orally/iv, 5 days 2. Ciprofloxacin, 500 mg /400 mg BD orally /iv, 5 days	No antibiotics unless complicated infection or immunocompromised host
E*scherichia coli* spp.		
STEC 0157	None	Avoid the use of antiperistaltics such as loperamide
ETEC	1. TMP-SMZ, 960 mg BD orally, 5 days 2. Ciprofloxacin, 500/400 mg BD orally /iv, 3 days or single dose 1000 mg orally	No antibiotics unless severe illness
EPEC, EIEC, EAEC	See ETEC	Clinically indistinguishable from ETEC
Vibrio cholerae O1 or O139	Doxycyclin, 300 mg single dose orally or TMP-SMZ, 960 mg BD orally, 3 days or ciprofloxacin, 1000 mg single dose orally	
Toxigenic *Clostridium difficile*	1. Metronidazole, 500 mg TD orally, 10 days 2. Vancomycin, 125 mg Q6h orally, 10 days	Interrupt offending antimicrobial regimen and isolate patient
Ribotype 027	Vancomycin, 250-500 mg Q6h orally, 10 days	First relapse: repeat same treatment Multiple relapses: tapered dosing regimen with vancomycin orally: after treatment: first week 125 mg Q6h, second week 125 mg BD, third week 125 mg OD, followed by 250-500 mg twice weekly for 1-2 weeks
Parasites		
Giardia lamblia	1. Tinidazole, 2 g single dose orally 2. Metronidazole, 2 g OD orally, 3 days	Tinidazole is (temporarily?) not available in the Netherlands Silent carrier state occurs relatively frequently and does not require treatment
Entamoeba histolytica	Metronidazole, 750 mg TD orally, 5-10 days or tinidazole, 2 g OD orally, 3 days	
Entamoeba histolytica carrier state	1. Paromomycin, 500 mg TD orally, 10 days 2. Clioquinol	Paromomycin is not registered in the Netherlands Effectiveness and dose unclear
Entamoeba dispar	None	Apathogenic
Cryptosporidium spp.	None	Any antibiotic regimen is disputed. Consider antibiotic treatment if immunocompromised or HIV+ with CD4 count < 150/mm^3: paromomycin 500 mg TD orally, 7 days
Cyclospora spp.	TMP-SMZ, 960 mg BD orally, 7 days	Immunocompromised host: TMP-SMZ 960 mg BD orally 10 days, followed by secondary prophylaxis: 960 mg OD, 3 times/week
Isospora spp.	None	Immunocompromised host: TMP-SMZ 960 mg BD orally 10 days, followed by secondary prophylaxis: 960 mg OD, 3 times/week

STEC = Shiga toxin-producing *E. coli*; ETEC = Enterotoxic *Escherichia coli*; EPEC = Enteropathogenic *E. coli*; EIEC = Enteroinvasive *E. coli*; EAEC = Enteroaggregative *E. coli*; HAART = highly active antiretroviral therapy; TMP-SMZ = trimethoprim-sulphamethoxazole (co-trimoxazole); OD = once daily; BD = twice daily; TD = thrice daily; Q6h = every six hours. *Taking into account the susceptibility of the cultured micro-organism.

EPIDEMIOLOGY

AID is commonly associated with a bacterial or viral infection, whereas chronic diarrhoea is more likely to be associated with parasitic disease.[3] In the Netherlands, approximately 300,000 people suffer from AID due to infection with *Campylobacter* species (spp.) every year and this is the most prominent bacterial cause of AID in our country.[4] In contrast to children below the age of 5, adults with community-acquired AID who seek medical help from a general practitioner are more likely to suffer from bacterial (mainly *Campylobacter* spp.) or parasitic disease

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(*Giardia lamblia*) than from viral disease. Noroviruses, formerly known as 'Norwalk-like' viruses, are the most common viral causative agents in adult community-acquired AID (*table 3*).

Table 3. *Epidemiology of acute infectious diarrhoea in Dutch general practices*[3]

Pathogen	Prevalence
Campylobacter	10.4/0.5
Salmonella	3.9/0.2
Shigella	0.1/0.0
Yersinia	0.7/1.1
STEC O157	0.5/0.6
Viruses	16.5/4.8
Parasites (incl. *G. lamblia*)	8.6/4.4

Percentage of patients/percentage healthy controls from all ages who tested positive for specified causative agent.

AID is the most frequent disease in travellers outside Europe: about 10 to 60% of them develop a more or less severe form of diarrhoea. The causative agents of traveller's AID are a subset of the agents responsible for AID in local communities, as there tend to be differences in exposure and immunity between travellers and residents. Enterotoxigenic *Escherichia coli* (ETEC) is the most important pathogen in traveller's AID, although enteroaggregative *E. coli* (EAEC) is believed to play an important causative role as well. In addition, *Campylobacter* spp. are 'emerging pathogens', as they are responsible for 15 to 25% of AID cases in travellers to Asia.[5,6] In travellers who have returned to the Netherlands with severe AID, the distribution of causative agents is likely to be different and it is reasonable to suppose that in this situation ETEC plays a far less important role, as ETEC-related disease tends to be mild and short lived.

Shiga toxin-producing *E. coli* (STEC) is the most important cause of haemorrhagic colitis and of kidney failure in children worldwide.[7] Cattle is the main reservoir for STEC and transmission occurs through consumption/ingestion of contaminated beef, water or (raw) milk. Although an estimated 1250 cases of STEC-related AID occur in the Netherlands every year, in 2003 only 40 cases were reported and 20 cases, mainly involving children, were complicated by the haemolytic uraemic syndrome (HUS). In patients with HUS, the O157:H7 strain is the predominant serotype.[8]

In the Western world, toxigenic *Clostridium difficile* infection is the main cause of nosocomial AID.[9] Hospital rooms can remain contaminated for a long period of time, as spores can survive outside the host for months. The disease is often transmitted via contaminated hands of healthcare workers. Although it is still generally accepted that a patient colonised with a toxigenic strain is not likely to develop *C. difficile*-associated disease (CDAD) until he or she is treated with antibiotics, recent publications on severe CDAD in healthy persons thought to be at low-risk suggest that CDAD epidemiology might be changing.[10-12] Although clindamycin, amoxicillin and cephalosporins are most commonly implicated – partially reflecting the extensive use of some of these drugs – almost all classes of antibiotics have been associated with CDAD. If AID develops after a stay of at least three days in a hospital, it is advised to avoid/interrupt the use of antibiotics and to carry out a proper diagnostic strategy for CDAD. This should include screening of a stool specimen for *C. difficile* toxins, since testing schemes that rely solely on *C. difficile* cultures yield a significant number of false-positive results (*figure 1*).[11]

TREATMENT OF IMPORTANT INDIVIDUAL PATHOGENS

In this section we will only discuss the most important pathogens briefly. Please refer to the complete guideline and *table 2* for detailed information.

Campylobacter

Infections with fluoroquinolone-resistant *Campylobacter* strains have become increasingly prevalent, coinciding with the introduction of fluoroquinolones in veterinary medicine.[13] Resistance data from 2002 and 2003, based on data from 16 regional laboratories in the Netherlands, reported high fluoroquinolone resistance rates amongst endemic *Campylobacter* isolates, ranging from 30.9% for *C. jejuni* to 39.2% for *C. coli*. For erythromycin, the resistance prevalence was 3.9 and 6.3%, respectively.[14]

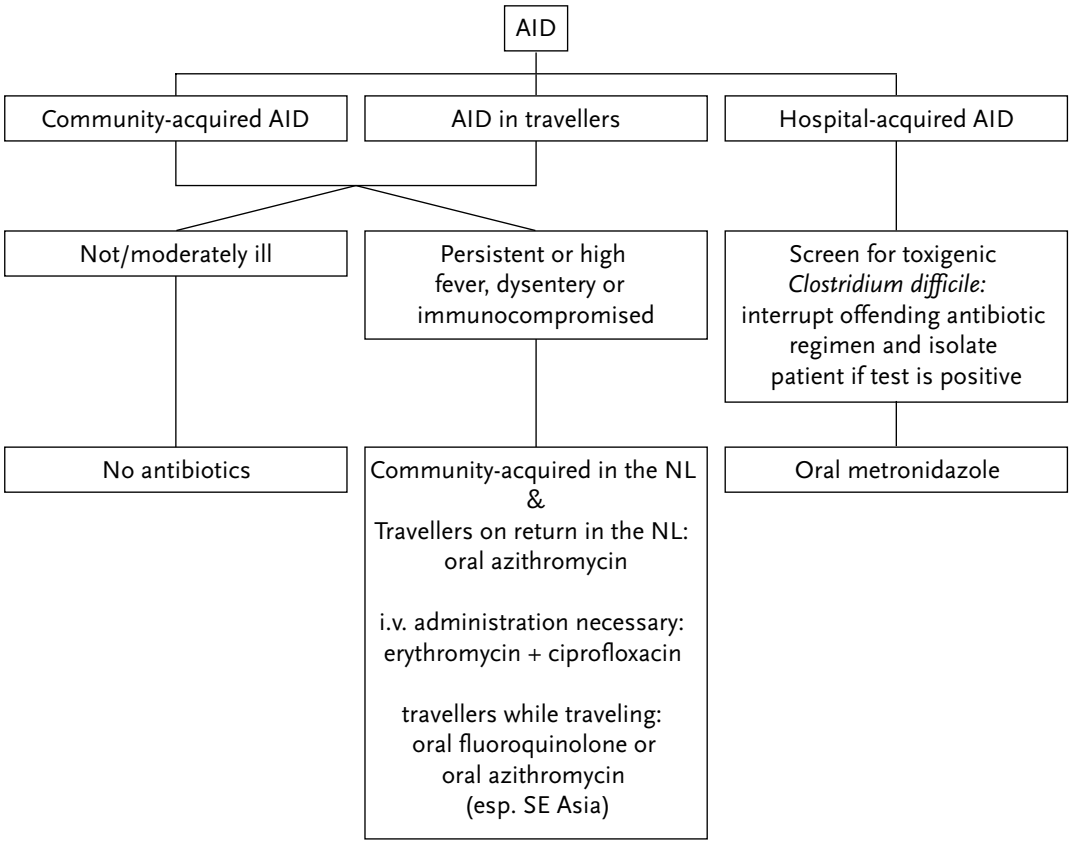
Analogous to the Dutch situation, many countries across Europe and the Americas, but especially in Southeast Asia, struggle with increasing fluoroquinolone resistance among *Campylobacter* spp, although regional differences are common. In a recent Thai study, a prevalence as high as 50 to 85% was found.[15] In this part of the world, not only *Campylobacter*, but also the other common causative agents of dysentery, such as *Shigella* spp. and nontyphoidal *Salmonella*, are becoming increasingly resistant to most agents commonly in use. The same study shows evidence of the emergence, although limited (6%), of combined resistance to fluoroquinolones and azithromycin among *Salmonella* and *Campylobacter* spp. Fluoroquinolone resistance rates of *Campylobacter* spp. isolated from travellers returning to the Netherlands are as high as 52.5% for *C. jejuni* and 59.1% for *C. coli*. The corresponding prevalence of erythromycin resistance is 2.7 and 10.5%, respectively.[14]

Salmonella

AID caused by nontyphoidal *Salmonella* spp., the second most frequently found bacterial pathogens in the Netherlands, is usually mild, although more severe

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Figure 1. *Flowchart showing empirical antimicrobial treatment for acute infectious diarrhoea (AID)*



systemic illness with metastatic infection may occur, especially in the elderly and immunocompromised.[16,17] Antibiotic treatment is not recommended, as the use of antibiotics has not proven to be effective in uncomplicated disease and may even have a negative effect on relapse risk and carrier state.[18-20] It is, however, recommended to start antibiotic treatment in case of severe illness or when the patient is immunocompromised, although scientific evidence is lacking. In this case, it is advised to use a potent bactericidal drug with intracellular activity, such as ciprofloxacin.[21] In 2003, fluoroquinolone resistance in human *Salmonella* spp. isolates in the Netherlands was reported to be almost nonexistent, although the prevalence of multiresistance against amoxicillin, doxycycline, TMP (-SMZ) and chloramphenicol was as high as 45%, depending on the serotype.[22,23]

Shiga toxin-producing *E. coli*

In Shiga toxin-producing *E. coli* (STEC)-related AID, antimicrobial therapy does not seem to affect the duration of diarrhoeal disease.[24] There are data that suggest a relationship between the use of antibiotics and HUS. In a prospective study in 2000, investigators found evidence for an increased risk for HUS when using antibiotics for STEC-related AID, but this conclusion could not be confirmed in a meta-analysis.[25] It is nevertheless advised to treat STEC-related AID strictly symptomatically. The use of loperamide should be avoided, as it may increase the risk of systemic disease.[26,27]

Toxigenic *C. difficile* and CDAD

The use of antibiotics is clearly associated with CDAD and discontinuation of the offending regimen may lead to recovery in 15 to 23% of cases. Antibiotic treatment is indicated for individuals with longstanding symptoms and for patients with an underlying disease. Hospitalised patients should be treated irrespective of the severity of the disease to prevent transmission. Oral metronidazole is considered to be the regimen of choice because it is effective, cheap and it does not carry a risk of colonisation and infection with vancomycin-resistant enterococci (VRE).[28,29] Oral vancomycin is regarded as equally effective, although some authors suggest that treatment with metronidazole may be more likely to fail.[30-32] A recent outbreak of a virulent strain of *C. difficile*, ribotype 027, in the Netherlands has led to controversy about the preferred first-line treatment.[33]

When taken orally for diarrhoea, metronidazole reaches bactericidal concentrations in faeces as a result of decreased absorption and active secretion by the infected intestinal epithelium. Consequently, the luminal concentration may

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decrease to an undetectable level when the diarrhoea resolves.[34] Although bactericidal faecal levels can be reached when metronidazole is given intravenously, the efficacy of the drug has only been established for oral administration.

Recurrent toxigenic *C. difficile* infection

Relapses of CDAD are common, occurring in 20 to 30% of patients initially treated successfully. Once a first relapse has occurred, the chance of getting multiple relapses increases to 45 to 65%.[29,35] Recurrent CDAD is hardly ever attributable to drug resistance and a first relapse can therefore be successfully treated with renewed administration of the same drug.[31] There is some evidence that multiple relapses are best treated with vancomycin in a 'tapered or pulsed dosing regimen': in a prospective study in 2002 including 163 patients with relapsing CDAD, tapered and pulsed dosing regimens with vancomycin and metronidazole were compared.[36] Patients treated with vancomycin had a better outcome compared with those treated with metronidazole, but the study was neither randomised nor controlled. The use of tapered or pulsed regimens is based on the idea that after discontinuation of therapy, spores may develop into vegetative stages, which can be killed by renewed exposure to vancomycin. Starting from the second relapse, we recommend a tapered dosing regimen with vancomycin for 19 to 25 days (*tables 1* and *2*).

Saccharomyces boulardii, a non-pathogenic yeast that can be isolated from lychees, has also been used for the treatment of (recurrent) CDAD. Animal studies have shown that prophylactic administration of *S. boulardii* can have a protective effect on the development of CDAD. In addition, the outcome of two prospective human trials supports the idea that adding *S. boulardii* to a standard antibiotic regimen can prevent recurrent CDAD, although the beneficial effect in the first study was limited to the subgroup of patients using the highest dose of vancomycin and the antibiotic regimens in the second study had not been standardised.[37,38] Not unimportantly, a few cases of disseminated *Saccharomyces cerevisiae* infections have been described since the introduction of *S. cerevisiae* as a probiotic drug.[39]

An adequate immune response to *C. difficile* toxins can protect against CDAD and relapses. Even though small studies suggest that the administration of intravenous and especially oral immunoglobulins against toxin A has a therapeutic effect on relapsing CDAD, it is still too early to recommend immunoglobulins as standard treatment.[40,41]

EMPIRICAL TREATMENT

Community-acquired AID

In patients with community-acquired AID presenting in general practice or at an outpatient clinic, a favourable effect has been noted on duration and severity of symptoms when antibiotic treatment with a fluoroquinolone is initiated within five days after the onset of the disease. The effect is independent of culture results. Most studies were performed with a five-day therapeutic regimen and therefore, at present, this should be regarded as the standard duration of therapy in the absence of appropriate diagnostic results.[42-44]

The favourable effect of fluoroquinolones must, however, be weighed against the aforementioned increase in *Campylobacter* resistance, which raises the concern that initial empirical treatment with ciprofloxacin is becoming increasingly inadequate. Whereas erythromycin can not be used for treating causative agents of AID other than *Campylobacter*, azithromycin can. Compared with erythromycin, the MIC_{90} of azithromycin for intestinal pathogens is at least eight times lower.[45,46] In addition, a number of studies have demonstrated the effectiveness of azithromycin for the treatment of AID caused by *Shigella*, *Campylobacter* and nontyphoidal *Salmonella* spp.[47,48] As *Salmonella* spp. have the ability to survive in macrophages, it is of major importance that *in vitro* and animal studies have shown that azithromycin achieves high intracellular concentrations and a bactericidal response for S*almonella* spp.[49] Furthermore, comparative human studies have shown that azithromycin is effective for the treatment of *Salmonella typhi* infections.[50,51] As a result of its pharmacokinetic profile this drug can be administered once daily.

Community-acquired AID in healthy adults, often of viral origin, is usually mild and short-lived, and empirical antibiotic treatment should therefore be restricted to individuals with high or long-standing fever, patients with dysentery and immunocompromised patients (*figure 1*). For these patient groups, we recommend a regimen of 500 mg azithromycin, once daily for three days. If intravenous treatment is necessary, a combination of ciprofloxacin and erythromycin, for five to seven days, may be used. As there is no clear evidence for a causative relationship between the use of antibiotics and HUS during STEC-related AID, there seems to be no reason to deny empirical antimicrobial treatment to an otherwise qualifying AID patient.

Traveller's diarrhoea

Multiple studies have demonstrated that antibiotics can limit the duration of symptoms in traveller's AID and recently this was confirmed in a Cochrane systematic review.[52] For years, TMP-SMZ has been the drug of empirical choice, but despite its low costs, its applicability is now greatly reduced due to worldwide resistance. Since the 1980s, fluoroquinolones have offered a new opportunity in antibiotic intervention and a three- to five-day course of ciprofloxacin can lead to a significant decrease in the duration of symptoms in adults, from three to five days to less than two days. A single-dose treatment is as effective as longer treatment courses.[53,54] In a study that involved American travellers to Mexico with AID, a single dose of azithromycin 1000 mg appeared to be

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as effective as a fluoroquinolone. Mild to moderate AID in healthy adult travellers does not require antibiotic treatment (*figure 1*).[55] Moderate AID or AID in immunodeficient travellers can be treated with fluoroquinolones, possibly in combination with loperamide. The favourable effect of this combination on duration of symptoms has proven to exceed the effect of an antibiotic alone.[56,57] In case of severe illness and/or dysentery, the use of loperamide is considered to be contraindicated. Depending on local epidemiology and resistance patterns, ciprofloxacin should be replaced by a single dose of azithromycin. At present, this seems to be mainly the case in Southeast Asia.

Because of the selection of pathogens mentioned earlier, patients with severe AID on return to the Netherlands should be treated according to the recommendations for community-acquired AID, with either azithromycin orally or a combination of erythromycin and ciprofloxacin intravenously.

NOTES

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