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bacteremia and in a patient with X-linked agammaglobulinemia

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Abstract: We describe a 15-year-old patient with X-linked agammaglobulinemia who developed malabsorption and bacteremia due to infection of Helicobacter pylori and Campylobacter jejuni. The Campylobacter bacteremia was only recognized after subculturing of blood culture bottles that failed to signal in the automated system. After 2 weeks treatment with meropenem and erythromycin for 4 weeks, the patient developed 10 months later a relapse of bacteremia with a high level erythromycin resistant C. jejuni. Sequencing revealed an A2058C mutation in 23S rRNA gene associated with this resistance. Treatment with doxycycline for 4 weeks finally resulted in complete eradication. This case report illustrates the importance for physicians to use adapted culture methods and adequate prolonged therapy in patients with an immunodeficiency. A summary of published case reports and series of patients with hypogammaglobulinemia or agammaglobulinemia with Campylobacter or Helicobacter bacteremia is given.

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Dear Dr. van Leeuwen,

Thank you for reviewing our manuscript entitled “Campylobacter jejuni bacteremia and Helicobacter pylori in a patient with X-linked agammaglobulinemia” (EJCMID-D-10-00198).

Hereby you find the revised version of our manuscript. We have considered all the points raised by the reviewer, and gave all the details of the way in which we have handled each of the points below.

We kindly ask you to reconsider our manuscript for publication in your journal.

Kind regards,

Robbert Bredius

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to Dr W. van Leeuwen, Reviews Editor

page 2

Answers to comments and questions from reviewer #1

- The reviewer suggested adding a sentence to the abstract to prompt physicians to use adapted culture methods and adequate prolonged therapy in the case of antibody deficient patients. Added in Abstract, page 4, line 10.
- Both in the Abstract and the text information is added to describe the microbiological work-up and a description of the antibiogram of the different strains. Added in Abstract, page 4, and the Case Report, page 6, line 17.
- We agree with the reviewer that the association of *Helicobacter* and *Campylobacter* infection in a child with XLA is rarely reported, and could be explained by the geographic origin of the patient. A comment including a new reference to address this is added. Added in the Discussion, page 8, line 17.
- We agree with the reviewer that immunoglobulin substitution of XLA patients should be aimed at higher through levels than we initially reached in this patient (see publication Eijkhout et al). A sentence stressing this is added in text, plus the reference to support this notion. Added in the Case Report, page 6 line 8 & Discussion, page 8, line 9.
- The possibility of neutropenia in XLA is indeed described. Our patient had normal neutrophil counts during the entire course of his disease; this is now added to the Case Report (page 6, line 21).
- Enterovirus infections are potential causes of gastrointestinal complaints and neurological abnormalities in XLA patients. Other pathogens were repeatedly searched for in the feces, blood and the cerebrospinal fluid but never found. In the Case Report the results of PCR, culture, et cetera are given (page 6, line 25 & page 7, line 15).

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1 **CAMPYLOBACTER JEJUNI BACTEREMIA AND HELICOBACTER PYLORI IN A PATIENT**
2 **WITH X-LINKED AGAMMAGLOBULINEMIA**

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40 **Running title:** *H. pylori* and *C. jejuni* in XLA
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ABSTRACT

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3 We describe a 15-year-old patient with X-linked agammaglobulinemia who developed malabsorption
4 and bacteremia due to infection of *Helicobacter pylori* and *Campylobacter jejuni*. The *Campylobacter*
5 bacteremia was only recognized after subculturing of blood culture bottles that failed to signal in the
6 automated system. After 2 weeks treatment with meropenem and erythromycin for 4 weeks, the patient
7 developed 10 months later a relapse of bacteremia with a high level erythromycin resistant *C. jejuni*.
8 Sequencing revealed an A2058C mutation in 23S rRNA gene associated with this resistance. Treatment
9 with doxycycline for 4 weeks finally resulted in complete eradication.

10 This case report illustrates the importance for physicians to use adapted culture methods and
11 adequate prolonged therapy in patients with an immunodeficiency. A summary of published case
12 reports and series of patients with hypogammaglobulinemia or agammaglobulinemia with
13 *Campylobacter* or *Helicobacter* bacteremia is given.

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16 **Keywords:** bacteremia, *Campylobacter jejuni*, *Helicobacter pylori*, hypogammaglobulinemia, X-
17 linked agammaglobulinemia.

INTRODUCTION

X-linked agammaglobulinemia (XLA) is a primary immunodeficiency caused by a mutation in the Bruton Tyrosine Kinase (*BTK*)-gene.[1] This defect leads to abnormal development of B-lymphocytes and hypogammaglobulinemia. Patients with XLA usually present with recurrent bacterial infections, mainly of the respiratory and gastrointestinal tract. Other bacterial infections, like cellulitis, arthritis, meningitis and sepsis have also been described, but are less common. Various case-reports mention a specific association of XLA patients and patients with acquired hypogammaglobulinemia with bacteremia caused by *Helicobacter* and *Campylobacter* species, see Table 1.[2;3]

Recently, we treated a boy with XLA who developed fever, loss of appetite and failure to thrive caused by a combination of *H. pylori* gastritis and recurrent *C. jejuni* bacteremia.

CASE REPORT

A five-year old Iranian boy with a history of recurrent infections and an absence of peripheral blood B-lymphocytes was diagnosed with XLA. The boy was living in The Netherlands since his fifth. DNA-analysis revealed a frame shift mutation (1614de1T) in exon 16 of the *BTK*-gene.[4] He was treated with prophylactic co-trimoxazole and intravenous immunoglobulin (IVIG) substitution therapy every 4 weeks. During the last 3 years, IgG levels varied from 5.0 to 8.7 g/L (normal range for IgG: 5.2 - 15.0 g/L). To reach a trough level of around 8 g/L he required a high dosage of IVIG of 1.2 g/kg.[5] He had no detectable IgA and IgM. At the age of 10 years he developed epilepsy caused by left occipital lesions, presumably acquired by infections in the past.

At the age of 15 years he was admitted to our hospital with progressive loss of appetite, initially ascribed to his anti-epileptic medication. He was severely malnourished (weight / length-ratio -3 Dutch Standard Deviation Score, comparable to Iranian growth charts). Stool antigen test for *H. pylori* was positive. Endoscopy and biopsies of the gastric antrum, corpus and duodenum showed chronic active inflammation with atrophy and intestinal metaplasia. Cultures of the antrum and corpus were positive for *H. pylori* as well as for *C. jejuni*. Biopsies of antrum and corpus were inoculated on non-selective blood agar media and onto specific *H. pylori* media (Pylori agar, Biomérieux, France) in a micro-aerophilic environment for 7 days. Identification was performed by conventional biochemical reactions according to standard operation procedures.[6] During hospitalization the patient had periods of fever. Laboratory tests showed an elevated C-reactive protein (up to 94 U/L; normal < 5 U/L). His leukocyte and neutrophil counts were always normal. Blood cultures revealed *C. jejuni*, sensitive for ciprofloxacin (MIC 0.032 mg/L), erythromycin (MIC 0.75 mg/L) and meropenem (MIC 0.012 mg/L) as determined by *E*-testing (AB Biomérieux, Solna, Sweden). An identical strain was isolated from patient's feces. Other pathogens were never detected from stool, throat, urine or spinal fluid; cultures or PCR tests were negative for enteric parasites, viruses including enteroviruses and pathogenic bacteria. The patient was treated with intravenous meropenem for two weeks, followed by oral erythromycin for another 4 weeks. Repeated blood cultures after ten days were negative. For eradication of *H. pylori* he additionally

1 received triple therapy with amoxicillin, clarithromycin and omeprazol for one week. *H. pylori* was
2 sensitive to erythromycin (MIC 0.38 mg/L), clarithromycin (MIC 0.19 mg/L) and meropenem (MIC
3 0.002 mg/L).

4 During follow-up he improved clinically and with tube feeding his weight increased to -1
5 Standard Deviation Score. Endoscopy was repeated eight months later and showed much less
6 inflammation of the gastric mucosa and absence of *H. pylori* in microscopy and culture of biopsies.
7 However, from a fecal specimen a *C. jejuni* strain was isolated with secondary resistance to
8 erythromycin (MIC \geq 256 mg/L) but persistent sensitivity to ciprofloxacin (MIC 0.125 mg/L) and
9 meropenem (MIC 0.008 mg/L). Ten months later, he again developed a *C. jejuni* bacteremia. The strain
10 had a similar pattern as the stool isolate, with high level resistance to erythromycin by *E*-testing (MIC \geq
11 256 mg/L), but the strain was sensitive to tetracycline. Sequence analysis of part of the 23S rRNA gene
12 revealed an A2058C mutation (position of nucleotide reported as the *Escherichia coli* equivalent),
13 known to be associated with erythromycin resistance.[7;8] The strain isolated 8 weeks earlier from the
14 feces did not have this mutation. No other pathogens were isolated. He again had complaints of loss of
15 appetite, no diarrhea or skin lesions and some weight loss. Co-trimoxazole prophylactic therapy was
16 switched to azithromycin (for 2 weeks) and later to doxycycline (for 4 weeks), which resulted in clinical
17 improvement and negative stool and blood cultures; now, with a follow-up of 6 months.

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DISCUSSION

In the primary antibody deficiency disorders such as XLA, enteropathogenic *Helicobacter* species and the closely related species *Flexispira* and *Campylobacter* can cause persistent gastrointestinal infections and bacteremia, as well as skin and bone infections.[2;3;9;10] In immunocompetent individuals bacteria are eliminated from the blood by antibody- and complement-mediated lysis. Patients with XLA form no or inadequate specific antibodies.[1;11] Despite immunoglobulin substitution therapy with normal IgG levels (IgA and IgM antibodies remained absent) severe infections with *Campylobacter* and *Helicobacter* can emerge.[11] Higher IgG through levels during immunoglobulin supplementation may lead to better protection.[5]

In the Netherlands the incidence of *Campylobacter* infections is 39 per 100.000 people per year (children and adults).[12] *C. jejuni* is the most frequently isolated pathogen of the *Campylobacter* species; *C. coli*, *C. lari* and *C. upsaliensis* are less frequently encountered pathogens. Transmission of *C. jejuni* occurs by ingestion of contaminated food (i.e. chicken and pork), water and unpasteurized milk. *Helicobacter* infections in children are acquired early in life, mainly via oral-fecal contact. In the Netherlands the prevalence of *H. pylori* in children is very low (1.2%); most infected children are offspring of non-Dutch parents like our patient.[13] Our patient had a double infection, which may be coincidental but could also be based on his Iranian background. In Iran, the prevalence of *H. pylori* was reported to be 58% in healthy 15 year old children.[14]

Bacteremia with *Campylobacter* and *Helicobacter* species is frequently found in XLA patients. Winkelstein et al.[2] found a prevalence of 10% in 21 septicemic patients from a series of 201 XLA patients. Recognition of bacteremia with *Helicobacter* and *Campylobacter* species is sometimes difficult, since *Helicobacter* and *Campylobacter* grow slowly in standard automatic blood culture-systems. It is recommended to subculture blood culture bottles to solid media after one week of incubation when no signal of growth has appeared. In some microbiological laboratories this is a standard procedure for blood culture bottles from patients with endocarditis or from patients with

1 hypogammaglobulinemia. In our patient the standard blood cultures were negative, only subculturing
2 resulted in recognition of *C. jejuni*.

3 Symptoms, antibiotic treatment, antibiotic resistance, and duration of bacteremia of published
4 cases are summarized in Table 1. Twenty-six immunocompromised patients with bacteremia caused by
5 *Campylobacter* or *Helicobacter* species have been described in the literature; only five of these cases
6 were children (< 18 years of age). Remarkably, diarrhea or other gastrointestinal complaints are not
7 always present (33 - 37%).[9] Erysipelas-like cellulitis was present in 11 of 26 patients (40%); it mostly
8 disappears within several days after start of antibiotic therapy but is an important early clinical sign for
9 *Helicobacter* or *Campylobacter* bacteremia. Five of 25 patients (20%) had septic arthritis or
10 osteomyelitis, which is remarkably high; others described an incidence of respectively 7% and 3% in
11 201 patients with XLA.[2]

12 Most patients needed prolonged antibiotic therapy to eradicate the microorganisms, with a
13 mean duration of approximately 10 months (ranging from 1 week to 3 years). Our patient presented
14 with fever, malaise and anorexia. He had a long lasting and recurrent bacteremia, which almost
15 exclusively appears in immunocompromised patients.

16 In immunocompetent individuals, *H. pylori* remains a superficial chronic gastritis, with a small
17 percentage of individuals progressing to duodenal or gastric ulcers and rarely to gastrointestinal
18 malignancies. Common variable immunodeficiency patients have an almost 50-fold increased risk for
19 gastric cancer and a 30-fold increased risk for lymphoma.[11] The patient we described did not develop
20 a relapse or recurrent *H. pylori* infection.

21 Antibiotic resistance of *Campylobacter* species to fluoroquinolones and macrolides is
22 increasing. In The Netherlands, resistance to fluoroquinolones and macrolides is up to 35% and 2.7% of
23 the isolates, respectively.[12] However, the latter may be overestimated, since phenotypical routine
24 susceptibility test for erythromycin are difficult to interpret.[15] Most *Campylobacter* isolates are
25 sensitive for amoxicillin-clavulanic acid (resistance rate 1 - 2%).[9] The strain of our patient had high-
26 level resistance to erythromycin (MIC \geq 256 mg/L). Because of reported difficulties in the phenotypic
27 recognition of erythromycin resistant isolates, the presence of the erythromycin resistant *C. jejuni* was

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1 confirmed by 23S rRNA gene sequence; analysis revealed an A2058C mutation.[7;15] *Campylobacter*
2 isolates displaying resistance to erythromycin usually have resistance-associated mutations at position
3 2058 and/or 2059 of the 23S rRNA gene. They lead to cross-resistance to macrolide and lincosamide
4 antibiotics. No resistance has been described for carbapenem antibiotics, such as meropenem.[9]

5 The mortality of inadequately treated bacteremia is estimated to be around 2.5 - 5.5%.[9] The
6 mean duration of treatment of bacteremia is 10 to 14 days in immunocompetent individuals. In
7 immunocompromised patients longer treatment may be necessary. Also, in our patient the
8 *Campylobacter* was hard to eradicate. He received two weeks intravenous treatment with meropenem,
9 followed by four weeks erythromycin with apparently good effect. However, despite changes of
10 antibiotic treatment *C. jejuni* remained detectable in his stool cultures, and later on he had a relapse of
11 bacteremia. After a four weeks course of doxycycline, *C. jejuni* could be eradicated.

12 In conclusion, multiple infections can be encountered in patients with XLA that present with
13 vague symptoms such as failure to thrive, weight loss or anorexia and fever. Bacteremia with
14 *Campylobacter* species is hard to detect and need specific laboratory expertise. In patients with
15 agammaglobulinemia *Campylobacter* eradication can only be achieved with adequate antibiotic therapy
16 and prolonged treatment; *H. pylori* seems easier to eliminate.

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FIGURE LEGEND

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2 1. Table 1. Summary of published case reports and series of patients with hypogammaglobulinemia or
3 XLA with Campylobacter or Helicobacter bacteremia.

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Table 1. Summary of published case reports and series of patients with hypogammaglobulinemia or XLA with *Campylobacter* or *Helicobacter* bacteremia

Reference	No (age in yrs)	Disease	Micro-organisms, sites other than blood	Resistance	Symptoms	Duration	Treatment, (number of relapses of bacteremia)
Le Bar, 1985 (10)	2 (24, 36)	Hypo	<i>C. jejuni</i> , Stool	NA	Fever, pneumonia, cellulitis	8 months (4), 6 months (1)	MC, AMG,
Spelman, 1986 (17)	2 (25, 29)	XLA	<i>C. jejuni</i>	NA	Cellulitis, fever, ureter colics		MC, AMG, 6 months (2)
van der Meer, 1986 (19)	1 (24)	XLA	<i>C. jejuni</i> , Stool	NA	Fever		NA, > 1 year (NA)
Chusid, 1987 (4)	1 (11)	XLA	<i>C. jejuni</i> , Stool	NA	Malaise		PEN, AMG, 1 week (0)
Kerstens, 1992 (9)	3 (26, 20, 24)	XLA, Hypo	<i>C. jejuni</i> , Stool, skin	FQ	Cellulitis, fever, osteomyelitis	1 month (1), 1 year (2), 1 year (2)	CA, MC,
Borleffs, 1993 (3)	2 (23, 25)	Hypo	<i>C. jejuni</i> , Stool	NA	Cellulitis, fever	6 months (2), 6 months (3)	CA, FQ, i.v. IgM,
Simon, 1995 (15)	1 (70)	Hypo	<i>C. jejuni</i>	NA	Arthritis, diarrhea		NA, Patient died
Autenrieth, 1996 (2)	1 (7)	XLA	<i>C. jejuni</i>	NA	Cellulitis		FQ, maternal plasma, > 2 years (NA)
Moore, 2001 (11)	1 (NA)	Hypo	<i>C. jejuni</i> , Stool	NA	Diarrhea		NA, 2 year (5)
Rafi, 2002 (14)	1 (32)	XLA	<i>C. jejuni</i> , Stool, colon, pericardial fluid	NA	Pericardial tamponade, pneumonia		MC, FQ, NA
Tokuda, 2004 (18)	1 (16)	XLA	<i>C. coli</i>	NA	Cellulitis		CA, AMG, 6 months (1)
Arai, 2007 (1)	1 (35)	XLA	<i>C. coli</i> , Stool	MC	Arthritis, fever		TET, CA, 1 year and 7 months (3)
Okada, 2008 (13)	1 (33)	XLA	<i>C. coli</i> , Intestinal biopsy	NA	Endocarditis, osteomyelitis		CA, FQ, TET, AMG, 8 months (4)
Chusid, 1990 (5)	1 (16)	Hypo	<i>C. upsaliens</i>	NA	Fever		Ceph, 6 months (1)
Neuzil, 1994 (12)	1 (50)	Hypo	<i>C. fetus</i>	NA	Osteomyelitis, cellulitis		CA, MC, 10 months (2)
Jirapongsananuruk, 2006 (8)	1 (15)	XLA	<i>C. lari</i>	Ceph, FQ	Sinusitis, fever		AMC, MC, 9 months (3)
Weir, 1999 (20)	1 (36)	XLA	<i>Flexispira rappini</i>	PEN, MC, Ceph, FQ	Cellulitis		AMG, CA, 3 years (NA)
Cuccherini, 2000 (6)	2 (36, 21)	XLA	<i>Helicobacter, flexispora</i> -like organism	Metr	Cellulitis, synovitis, fever, gastritis		AMG, CA, 1 year (NA)
Gerrard, 2001 (7)	1 (27)	XLA	<i>H. canis, Flexispora rappini</i>	NA	Cellulitis, fever		TET, Metr, 2 months (1)
Simons, 2004 (16)	1 (54)	XLA	<i>H. cinaedi</i>	NA	Cellulitis		AMG, CA, 3 months (2)
van den Bruele, this paper	1 (15)	XLA	<i>C. jejuni, H. pylori</i> , stool	MC	Fever, anorexia		CA, MC, TET, 10 months (1)

Legend: XLA = X-linked agammaglobulinemia, Hypo = hypoagammaglobulinemia, NA = not available, i.v. IgM = intravenous immunoglobulin M, AMC = amoxicillin/clavulanic acid, AMG = aminoglycoside, CA = carbapenem, Ceph = cephalosporin, FQ = fluoroquinolone, MC = macrolide, Metr = metronidazole, PEN = penicillin, TET = tetracycline

* For the references of Table 1 we refer to Supplemental Material 1.

Electronic Supplementary Material

[Click here to download Electronic Supplementary Material: References table 1.doc](#)