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1 ***Clostridium difficile* associated reactive arthritis: case report and**
2 **literature review**

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24 **ABSTRACT**

25 Introduction: Extra-gastro-intestinal tract manifestations associated with *Clostridium difficile*
26 infection (CDI), including reactive arthritis (ReA), are uncommon.

27 Method: We report a case of ReA associated with a relapse of CDI in a 46-year-old woman. A
28 toxigenic *C. difficile* strain was isolated from stools and characterized as PCR-ribotype 014/020/077.
29 We conducted a comprehensive literature review of ReA associated with CDI (ReA-CDI). Diagnostic
30 criteria for ReA-CDI were: (i) evidence of aseptic synovitis (confirmed by culture) developing during
31 or immediately after colitis, (ii) presence of a toxigenic *C. difficile* strain in stool samples, and (iii)
32 absence of other causes of colitis and arthritis.

33 Results: Forty-nine cases of ReA-CDI (excluding the present report) have already been described since
34 1976. Of these reports, Mean age of patients was 38 years (SD: 18.5), 46% were male, and 68% had
35 HLA B27 genotype. Sixty-nine percent of patients received a β -lactamin treatment before CDI. ReA-
36 CDI occurred a median 10 days (range 0-55 days) after CDI. Outcome was favorable in 90% of
37 patients and oral non anti-inflammatory drugs were required for 55%.

38 Conclusion: ReA-CDI remains uncommon. Compared to the general population, it is more likely
39 observed in younger patients with HLA B27-positive genotype.

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56 INTRODUCTION

57 *Clostridium difficile* (CD) is a strict anaerobic, spore-forming, gram positive bacillus. Only toxigenic
58 strains of CD are involved in gastro-intestinal tract infections. Clinical symptoms associated with CD
59 infections (CDI) generally range from mild diarrhea to severe pseudomembranous colitis (PMC). CDI
60 is defined by several signs and symptoms, presence of CD toxin and/or toxin-producing CD in stools,
61 and no other causes of PMC after colonoscopic or histopathological evaluation [1]. The incidence of
62 CDI is increasing in many countries worldwide and CD has a considerable burden on healthcare
63 systems [2]. In particular, the United States Center for Disease Control and Prevention (CDC) recently
64 placed CDI among bacterial infections posing the highest health risk due to antimicrobial resistance
65 [3].

66 In Europe, the incidence of healthcare-associated CDI is 4.2 per 10,000 patient-days, with a case-
67 fatality rate of 9% within three months after diagnosis [4]. In the United States, there was a total of
68 453,000 estimated number of CDIs in 2011 based on data from active population- and laboratory-
69 based surveillance [2]. Antibiotic use, advanced age, and comorbidities (liver cirrhosis, heart disease,
70 pulmonary disease, chronic dialysis, immunocompromised status) are the most common risk factors
71 associated with CDI [4].

72 Extra-colonic CDI have been described in previous reports and include bacteremia [5], cellulitis [4],
73 pancreatic [6] or splenic abscesses [7], pleural empyema [8], osteomyelitis [5], native or artificial joint
74 [9,10], or appendicitis [10]. Extra-colonic manifestations have also been observed, such as uremic
75 and hemolytic syndrome [11,12] and reactive arthritis (ReA), yet are probably unrelated to bacteria
76 itself.

77 Birnbaum *et al.* proposed diagnostic criteria for ReA associated with CDI (ReA-CDI) [13], which
78 include the following: i) evidence of aseptic synovitis (confirmed by culture) developing during or
79 immediately after colitis, (ii) presence of toxins produced by *C. difficile* in stool samples, and (iii)
80 absence of other causes of colitis and arthritis. The pathophysiology of Rea-CDI is poorly understood,
81 while the underlying cause of its occurrence remains unknown.

82 We report herein a case of ReA-CDI observed in a 46-year-old woman and present a comprehensive
83 review of previous cases in the literature.

84

85 CASE REPORT

86 A 46-year-old Caucasian woman was admitted to Saint-Antoine Hospital (Paris, France), for an acute
87 episode of antibiotic-associated diarrhea.

88 She experienced iterative lower urinary tract infections (UTI) and chronic anemia due to iron
89 deficiency. She reported no particular medication intake, no smoking, and no drug or alcohol use.
90 She had no family history of or symptoms related to autoimmune disease.

91 Seven months before hospitalization, she had foot surgery as a result of hallux valgus. She reported
92 large quantities of aqueous diarrhea that resolved after 10-day treatment with oral metronidazole.
93 Stool testing was not performed at that time. Three weeks later, she developed oligoarthritis (both
94 ankles and left knee), which lasted roughly 5 months and resolved during treatment with
95 ketoprofene.

96 A few days prior to hospitalization, she was treated for a lower UTI with a two-day course of cefixim.
97 She was admitted to the emergency room for severe diarrhea, vomiting and abdominal pain. Clinical
98 examination revealed arterial pressure at 82/54mmHg (which was comparable to previous
99 measures), tachycardia (110 bpm) and no other abnormalities. CD was detected in stool samples by
100 enzyme immunoassay (GDH, Cdiff Quik Chek[®], Alere) and confirmed by polymerase chain reaction
101 (PCR) toxin B detection (GenXpert[®], Cepheid) but not with a cell culture cytotoxicity assay. She
102 underwent rehydration therapy and initiated a 10-day course of oral metronidazole. She had rapid
103 clinical improvement and was discharged 2 days later.

104 She was readmitted 11 days after discharge for oligoarthritis (both ankles and left knee), fever (38.
105 1°C), myalgia, and recurrence of diarrhea. Upon examination, both of her ankles and left knee were
106 slightly swollen and painful. Stool samples tested positive for toxinogenic CD again, while this time
107 the cell culture cytotoxicity assay was positive. Strains from both the first and second episodes were
108 genotyped as PCR-ribotype 014/020/077.

109 Joint X-ray was normal. Blood and urine culture were sterile. Complete blood count was normal
110 except for lymphocyte count at 1326 cells/mm³, hemoglobin at 11.3g/dL, and platelet count at
111 483,000/mm³. There were no other ion (including calcium) or renal abnormalities. C-reactive protein
112 level was 114.6mg/L, plasmatic protein electrophoresis demonstrated pro-inflammation (increase in
113 α -1, α -2 and γ -globulins). An intra-articular puncture of the knee was performed and showed high
114 degrees of inflammation with 10,000 elements/mm³, including 7300/mm³ polymorphic neutrophils,
115 while no crystals were identified. Articular fluid was placed in bacteriological cultures, including
116 incubation in anaerobic blood culture, which were negative.

117 Oral vancomycin 125mg was given four times daily for 10 days to treat CDI. Afterwards, paracetamol
118 and tramadol were administered to treat probable ReA-CDI. Arthritis and diarrhea fully resolved
119 within 3 weeks. At the one-year follow-up visit, no recurrence of diarrhea or arthritis was reported.

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121 REVIEW

122 We performed a review of all ReA-CDI cases published in the literature. We searched for the
123 combined terms “Reactive arthritis” and “*Clostridium difficile*” in PubMed and obtained 41 articles
124 amounting to 51 cases of ReA-CDI. We excluded 2 patients who did not have toxin detected in stool
125 samples, per definition of CDI [15]. In total, we summarize 39 articles including 49 cases of ReA-CDI,
126 all of which were reported among adults and children since 1976 [14,16–49] (**Table 1**).

127 Patients had a mean age of 38 years (SD: 18.5) and were mostly females (54%). Patients were
128 noticeably younger than those included in a European survey of 2011 but the proportion of females
129 was similar (56%) [4]. HLA B27 genotype was observed in 28/41 patients (68%, 95%CI: 53.7 %-82.3
130 %).

131 First-line treatment of CDI was metronidazole in 13/24 (54.2%, 95%CI: 27.1-81.3%) and oral
132 vancomycin in 11/24 cases (45.8%, 95%CI: 16.4-75.2%).

133 ReA occurred a median 10 days after CDI (range: 0-55 days). Of all 50 cases, initial presentation was
134 monoarthritis in 9 (18%, 95%CI: 7.4-28.6%), oligoarthritis in 22 (44%, 95%CI: 30.2-57.8), and
135 polyarthritis in 19 (38%, 95%CI: 24.5-51.5%). The two joints most frequently involved in ReA-CDI
136 were ankles (63.6%, 95%CI: 45.8-81.4%) and knees (59.1%, 95%CI: 40.2-78%). ReA-CDI lasted from 5-
137 800 days (median=42 days). Clinical outcome was favorable in 38/42 cases (90.5%, 95%CI: 81.6-99.4
138 %) as non steroid anti-inflammatory drugs were needed in 11/20 cases (55%, 95%CI: 33.2-76.8 %). No
139 reoccurrence of CDI was described in the literature.

140 None of the 49 cases presented in this review reported the specific ribotype strain involved in CDI.
141 The patient in our case report was infected with CD PCR-ribotype 014/020/077, one of the most
142 frequent strains in France and Europe [50,51]. Further studies exploring a possible association
143 between ReA and CD strain would be helpful in this context.

144 There are few data regarding the pathological mechanism involved in ReA-CDI. It could be
145 hypothesized that immunologic tolerance is interrupted during antigenic presentation and
146 contributes to ReA-CDI. Indeed, a major bacterial structure, lipopolysaccharide (LPS), is commonly
147 found in the blood of patients with ReAs before the onset of arthritis, owing to other entero-invasive

148 pathogens such as *Salmonella* sp or *Chlamydia trachomatis* [52]. As CD is devoid of LPS, it remains to
149 be demonstrated if other sources of circulating LPS or CD-antigen are present before the onset of
150 ReA-CDI. CD-toxin A is known to increase permeability of the epithelial intestinal barrier [28]. As a
151 result, CD-antigen and/or LPS from other gram-negative bacteria could reach blood circulation via
152 the gut, driving an antigenic reaction and disrupting immunologic tolerance. Activated autoreactive T
153 lymphocytes could then reach cartilage tissue and cause synovitis. Moreover, LPS from *Escherichia*
154 *coli* is able to enhance the cytotoxicity activity of CD toxin A [54].

155 The hypothesis of antigenic presentation is also supported by the association between ReA-CDI and
156 HLA B27 [54] and the high prevalence of HLA B27 patients in our review, compared to the general
157 population, argues for a predisposition to ReA. Even patients without HLA B27 genotype were able to
158 resolve ReA-CDI without any antibiotic treatment, providing corroborating evidence for non-septic
159 arthritis. Unfortunately, we could not determine the HLA status of our patient.

160 Importantly, CD septic arthritis can only be excluded if there is no CD identified in the synovial fluid.
161 In the literature, 28 negative articular liquid cultures were reported, on which only one CD-toxin PCR
162 was performed [48]. In our opinion, the argument for a ReA-CDI diagnosis should require additional
163 laboratory testing, such as specific culture for CD by toxin detection and 16S RNA analysis from
164 articular liquid.

165 Even if the mechanisms underlying extra-colonic manifestations are unclear, some molecules like
166 calprotectin (CP), interleukin (IL)-8 or IL-23 may play an important role in ReA-CDI [55]. CP is a
167 calcium- and zinc-binding protein released from the cytosol after neutrophil activation [56]. CP has
168 antibacterial, apoptosis-inducing, leukocyte-chemotactic properties and is a potential biomarker of
169 inflammation [57], especially during inflammatory bowel disease's flare ups [59]. Fecal CP levels have
170 also demonstrated strong correlation with neutrophil excretion in stool [60]. CP levels in the plasma
171 and synovial fluid are also high during rheumatoid arthritis [61] and ReA [62]. CP has also been
172 quantified in synovial tissue of rheumatoid arthritis patients, specifically in the lining adjacent to the
173 cartilage-pannus junction, which is the primary site of cartilage destruction and bone erosion [61]. Of
174 note, elevated levels of CP are also found in the feces of patients with CDI [58]. Further studies
175 quantifying CP in plasma and synovial fluid from ReA-CDI patients would be worthwhile in order to
176 elucidate its potential role.

177

178 **CONCLUSION**

179 We reported a case of ReA-CDI and analyzed 49 other cases of ReA-CDI published in the literature.
180 Further studies are needed to determine the underlying pathophysiological mechanism behind ReA-
181 CDI, while developing the role of specific ribotypes and CP.

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- 204 1. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, et al. Clinical practice
205 guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare
206 epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect
207 Control Hosp Epidemiol. 2010 May;31(5):431–55.
- 208 2. Lessa FC, Winston LG, McDonald LC, Emerging Infections Program C. difficile Surveillance Team.
209 Burden of Clostridium difficile infection in the United States. N Engl J Med. 2015 Jun
210 11;372(24):2369–70.
- 211 3. CDC - Clostridium difficile Infection - HAI [Internet]. [cited 2015 Jul 7]. Available from:
212 http://www.cdc.gov/HAI/organisms/cdiff/Cdiff_infect.html
- 213 4. Bauer MP, Notermans DW, van Benthem BHB, Brazier JS, Wilcox MH, Rupnik M, et al.
214 Clostridium difficile infection in Europe: a hospital-based survey. Lancet Lond Engl. 2011 Jan
215 1;377(9759):63–73.
- 216 5. Bhargava A, Sen P, Swaminathan A, Ogbolu C, Chechko S, Stone F. Rapidly progressive
217 necrotizing fasciitis and gangrene due to Clostridium difficile: case report. Clin Infect Dis Off
218 Publ Infect Dis Soc Am. 2000 Jun;30(6):954–5.
- 219 6. Riley TV, Karthigasu KT. Chronic osteomyelitis due to Clostridium difficile. Br Med J Clin Res Ed.
220 1982 Apr 24;284(6324):1217–8.
- 221 7. Sofianou DC. Pancreatic abscess caused by Clostridium difficile. Eur J Clin Microbiol Infect Dis
222 Off Publ Eur Soc Clin Microbiol. 1988 Aug;7(4):528–9.
- 223 8. Kumar N, Flanagan P, Wise C, Lord R. Splenic abscess caused by Clostridium difficile. Eur J Clin
224 Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol. 1997 Dec;16(12):938–9.
- 225 9. Simpson AJ, Das SS, Tabaqchali S. Nosocomial empyema caused by Clostridium difficile. J Clin
226 Pathol. 1996 Feb;49(2):172–3.
- 227 10. Libby DB, Bearman G. Bacteremia due to Clostridium difficile--review of the literature. Int J
228 Infect Dis IJID Off Publ Int Soc Infect Dis. 2009 Sep;13(5):e305–9.
- 229 11. Vaishnavi C. Clostridium difficile infection: clinical spectrum and approach to management.
230 Indian J Gastroenterol Off J Indian Soc Gastroenterol. 2011 Dec;30(6):245–54.

- 231 12. Mbonu CC, Davison DL, El-Jazzar KM, Simon GL. Clostridium difficile colitis associated with
232 hemolytic-uremic syndrome. Am J Kidney Dis Off J Natl Kidney Found. 2003 May;41(5):E14.
- 233 13. Alvarado AS, Brodsky SV, Nadasdy T, Singh N. Hemolytic uremic syndrome associated with
234 Clostridium difficile infection. Clin Nephrol. 2014 Apr;81(4):302–6.
- 235 14. Birnbaum J, Bartlett JG, Gelber AC. Clostridium difficile: an under-recognized cause of reactive
236 arthritis? Clin Rheumatol. 2008 Feb 1;27(2):253–5.
- 237 15. Leffler DA, Lamont JT. Clostridium difficile Infection. N Engl J Med. 2015 Apr 16;372(16):1539–
238 48.
- 239 16. Rothschild BM, Masi AT, June PL. Arthritis associated with ampicillin colitis. Arch Intern Med.
240 1977 Nov;137(11):1605–6.
- 241 17. Fairweather SD, Youngs D, George RH, Burdon DW, Keighley MR. Arthritis in
242 pseudomembranous colitis associated with an antibody to Clostridium difficile toxin. J R Soc
243 Med. 1980 Jul;73(7):524–5.
- 244 18. Bolton RP, Wood GM, Losowsky MS. Acute arthritis associated with Clostridium difficile colitis.
245 Br Med J Clin Res Ed. 1981 Oct 17;283(6298):1023–4.
- 246 19. Abbott WG, Caughey DE. Reactive arthritis due to Clostridium difficile. N Z Med J. 1982 Apr
247 28;95(706):287.
- 248 20. Puddey IB. Reiter's syndrome following antibiotic-associated colitis. Aust N Z J Med. 1982
249 Jun;12(3):292–3.
- 250 21. McCluskey J, Riley TV, Owen ET, Langlands DR. Reactive arthritis associated with Clostridium
251 difficile. Aust N Z J Med. 1982 Oct;12(5):535–7.
- 252 22. Lofgren RP, Tadlock LM, Soltis RD. Acute oligoarthritis associated with Clostridium difficile
253 pseudomembranous colitis. Arch Intern Med. 1984 Mar;144(3):617–9.
- 254 23. Caroli A, Cecchetto G, Sardeo G, Volpi A. [Acute reactive arthritis in pseudomembranous
255 colitis]. Recenti Prog Med. 1986 Jun;77(6):316–8.

- 256 24. Paty JG, Nichols RE. Arthritis and non-antibiotic-associated pseudomembranous colitis. *Arthritis*
257 *Rheum.* 1987 Sep;30(9):1075–6.
- 258 25. Atkinson MH, McLeod BD. Reactive arthritis associated with *Clostridium difficile* enteritis. *J*
259 *Rheumatol.* 1988 Mar;15(3):520–2.
- 260 26. Hannonen P, Hakola M, Möttönen T, Oka M. Reactive oligoarthritis associated with *Clostridium*
261 *difficile* colitis. *Scand J Rheumatol.* 1989;18(1):57–60.
- 262 27. Mermel LA, Osborn TG. *Clostridium difficile* associated reactive arthritis in an HLA-B27 positive
263 female: report and literature review. *J Rheumatol.* 1989 Jan;16(1):133–5.
- 264 28. Cope A, Anderson J, Wilkins E. *Clostridium difficile* toxin-induced reactive arthritis in a patient
265 with chronic Reiter's syndrome. *Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol.*
266 1992 Jan;11(1):40–3.
- 267 29. Putterman C, Rubinow A. Reactive arthritis associated with *Clostridium difficile*
268 pseudomembranous colitis. *Semin Arthritis Rheum.* 1993 Jun;22(6):420–6.
- 269 30. Sensini A, Marroni M, Bassotti G, Farinelli S, D'Alò F, Gentili AM, et al. *Clostridium difficile*-
270 associated reactive arthritis in an HLA-B27 negative male. *J Clin Gastroenterol.* 1993
271 Jun;16(4):354–5.
- 272 31. Guillemin P, Gerster JC. [Reactive arthritis induced by *Clostridium difficile* enteritis]. *Praxis.*
273 2005 Mar 23;94(12):471–4.
- 274 32. Keating RM, Vyas AS. Reactive arthritis following *Clostridium difficile* colitis. *West J Med.* 1995
275 Jan;162(1):61–3.
- 276 33. Rochet N. Rheumatic manifestations of pseudomembranous colitis. *Rev Rhum Engl Ed.* 1995
277 Mar;62(3):223.
- 278 34. Wright TW, Linscheid RL, O'Duffy JD. Acute flexor tenosynovitis in association with *Clostridium*
279 *difficile* infection: a case report. *J Hand Surg.* 1996 Mar;21(2):304–6.
- 280 35. Cron RQ, Gordon PV. Reactive arthritis to *Clostridium difficile* in a child. *West J Med.* 1997
281 Jun;166(6):419–21.

- 282 36. Nikkari S, Yli-Kerttula U, Toivanen P. Reactive arthritis in a patient with simultaneous parvovirus
283 B19 infection and Clostridium difficile diarrhoea. *Br J Rheumatol*. 1997 Jan;36(1):143–4.
- 284 37. Löffler HA, Pron B, Mouy R, Wulffraat NM, Prieur A-M. Clostridium difficile-associated reactive
285 arthritis in two children. *Jt Bone Spine Rev Rhum*. 2004 Jan;71(1):60–2.
- 286 38. Veillard E, Guggenbuhl P, Bello S, Lamer F, Chalès G. Reactive oligoarthritis in a patient with
287 Clostridium difficile pseudomembranous colitis. Review of the literature. *Rev Rhum Engl Ed*.
288 1998 Dec;65(12):795–8.
- 289 39. Koçar IH, Çalışkaner Z, Pay S, Turan M. Clostridium difficile infection in patients with reactive
290 arthritis of undetermined etiology. *Scand J Rheumatol*. 1998;27(5):357–62.
- 291 40. Söderlin MK, Alasaarela E, Hakala M. Reactive arthritis induced by Clostridium difficile enteritis
292 as a complication of Helicobacter pylori eradication. *Clin Rheumatol*. 1999;18(4):337–8.
- 293 41. Vermeulen C, Lemaire V, Lioté F. [Joint manifestations related to Clostridium difficile]. *Presse*
294 *Médicale Paris Fr* 1983. 2000 Mar 11;29(9):476–81.
- 295 42. Razavi B. Reactive arthritis after Helicobacter pylori eradication. *Lancet*. 2000 Feb
296 26;355(9205):720.
- 297 43. Jacobs A, Barnard K, Fishel R, Gradon JD. Extracolonic manifestations of Clostridium difficile
298 infections. Presentation of 2 cases and review of the literature. *Medicine (Baltimore)*. 2001
299 Mar;80(2):88–101.
- 300 44. Miner J, Gillan MM, Alex P, Centola M. Steroid-refractory ulcerative colitis treated with
301 corticosteroids, metronidazole and vancomycin: a case report. *BMC Gastroenterol*. 2005;5:3.
- 302 45. Ducroix-Roubertou S, Genet C, Rogez JP, Weinbreck P, Denes E. [Reactive arthritis due to
303 Clostridium difficile]. *Médecine Mal Infect*. 2005 Aug;35(7-8):419–21.
- 304 46. Durand MJ, Gutterman DD. Diversity in Mechanisms of Endothelium-Dependent Vasodilation in
305 Health and Disease. *Microcirc N Y N* 1994. 2013 Apr;20(3):239–47.
- 306 47. Durand CL, Miller PF. Severe Clostridium difficile colitis and reactive arthritis in a ten-year-old
307 child. *Pediatr Infect Dis J*. 2009 Aug;28(8):750–1.

- 308 48. Ben Abdelghani K, Gerard-Dran D, Morel J, Combe B. [Clostridium difficile associated reactive
309 arthritis]. Rev Médecine Interne Fondée Par Société Natl Francaise Médecine Interne. 2010
310 Mar;31(3):e13–5.
- 311 49. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case
312 19-1998. A 70-year-old man with diarrhea, polyarthritis, and a history of Reiter's syndrome. N
313 Engl J Med. 1998 Jun 18;338(25):1830–6.
- 314 50. Eckert C, Coignard B, Hebert M, Tarnaud C, Tessier C, Lemire A, et al. Clinical and
315 microbiological features of Clostridium difficile infections in France: The ICD-RAISIN 2009
316 national survey. Médecine Mal Infect. 2013 Feb;43(2):67–74.
- 317 51. Davies KA, Longshaw CM, Davis GL, Bouza E, Barbut F, Barna Z, et al. Underdiagnosis of
318 Clostridium difficile across Europe: the European, multicentre, prospective, biannual, point-
319 prevalence study of Clostridium difficile infection in hospitalised patients with diarrhoea
320 (EUCLID). Lancet Infect Dis. 2014 Dec;14(12):1208–19.
- 321 52. Granfors K, Jalkanen S, Lindberg AA, Mäki-Ikola O, von Essen R, Lahesmaa-Rantala R, et al.
322 Salmonella lipopolysaccharide in synovial cells from patients with reactive arthritis. Lancet Lond
323 Engl. 1990 Mar 24;335(8691):685–8.
- 324 53. Sánchez-Hurtado K, Poxton IR. Enhancement of the cytotoxic activity of Clostridium difficile
325 toxin A by surface-associated antigens. J Med Microbiol. 2008 Jun;57(Pt 6):739–44.
- 326 54. Prati C, Bertolini E, Toussirot E, Wendling D. Reactive arthritis due to Clostridium difficile. Jt
327 Bone Spine Rev Rhum. 2010 Mar;77(2):190–2.
- 328 55. Darkoh C, Turnwald BP, Koo HL, Garey KW, Jiang Z-D, Aitken SL, et al. Colonic
329 Immunopathogenesis of Clostridium difficile Infections. Clin Vaccine Immunol CVI. 2014
330 Apr;21(4):509–17.
- 331 56. Vaos G, Kostakis ID, Zavras N, Chatzemichael A. The role of calprotectin in pediatric disease.
332 BioMed Res Int. 2013;2013:542363.
- 333 57. Bressler B, Panaccione R, Fedorak RN, Seidman EG. Clinicians' guide to the use of fecal
334 calprotectin to identify and monitor disease activity in inflammatory bowel disease. Can J
335 Gastroenterol Hepatol. 2015 Jun 30;

- 336 58. Konikoff MR, Denson LA. Role of fecal calprotectin as a biomarker of intestinal inflammation in
337 inflammatory bowel disease. *Inflamm Bowel Dis*. 2006 Jun;12(6):524–34.
- 338 59. Røseth AG, Schmidt PN, Fagerhol MK. Correlation between faecal excretion of indium-111-
339 labelled granulocytes and calprotectin, a granulocyte marker protein, in patients with
340 inflammatory bowel disease. *Scand J Gastroenterol*. 1999 Jan;34(1):50–4.
- 341 60. Hammer HB, Ødegaard S, Fagerhol MK, Landewé R, van der Heijde D, Uhlig T, et al. Calprotectin
342 (a major leucocyte protein) is strongly and independently correlated with joint inflammation
343 and damage in rheumatoid arthritis. *Ann Rheum Dis*. 2007 Aug;66(8):1093–7.
- 344 61. Hammer HB, Kvien TK, Glennås A, Melby K. A longitudinal study of calprotectin as an
345 inflammatory marker in patients with reactive arthritis. *Clin Exp Rheumatol*. 1995 Feb;13(1):59–
346 64.
- 347 62. Swale A, Miyajima F, Roberts P, Hall A, Little M, Beadsworth MBJ, et al. Calprotectin and
348 lactoferrin faecal levels in patients with *Clostridium difficile* infection (CDI): a prospective
349 cohort study. *PLoS One*. 2014;9(8):e106118.

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AUTHOR YEAR OF PUBLICATION	SEX	AGE (years)	HLA B27	REASON FOR PRESCRIBING ATB BEFORE CDI	ATB BEFORE CDI	ATB USED TO TREAT CDI	TUI (days)	LOCATION OF ARTHRITIS	OUTCOME	SYMPTOM DURATION (days)
Rollins <i>et al.</i> 1976	M	55	NA	ENT infection	β -lact	NA	35	Elbow, Wrist, Knee, Foot	NA, Resolution	5
Rothschild <i>et al.</i> 1977	F	23	NA	Genital infection	β -lact	NA	8	Knee	NA, Resolution	5
Fairweather <i>et al.</i> 1980	F	53	NA	Prophylaxis	Linc	NA	15	Wrist, Hip, Ankle, Foot	NSAID, Resolution	10
Bolton <i>et al.</i> 1981	F	45	-	Skin infection	Linc	IMDZ	21	Knee, Ankle	NSAID, Resolution	43
Abbott <i>et al.</i> 1982	F	27	-	NA	β -lact	NA	8	Elbow, Wrist, Knee	NA, Resolution	42
Puddey <i>et al.</i> 1982	M	48	+	Skin infection	β -lact	NA	16	Knee	NA, Resolution	56
McCluskey 1982	F	37	+	Skin infection	Linc	NA	14	Wrist, Knee, Ankle	NA, Resolution	29
Lofgren <i>et al.</i> 1984	M	61	+	Prophylaxis	β -lact	GLP	11	Hip, Knee	0, Resolution	14
Caroli <i>et al.</i> 1986	M	77	+	Respiratory infection	β -lact	NA	8	Knee	NA	NA
Paty <i>et al.</i> 1987	F	28	-	0	0	NA	28	Wrist, Hand, Knee, Ankle	NA, Resolution	21
Atkinson <i>et al.</i> 1988	M	22	-	Prophylaxis	β -lact	NA	0	Shoulder, Wrist, Ankle	NA, Resolution	200
Atkinson <i>et al.</i> 1988	M	44	+	Skin infection	β -lact	NA	16	Knee, Ankle	NA, Resolution	22
Hannonen <i>et al.</i> 1989	F	23	+	Other	Linc	NA	10	Wrist, Hand, Knee	NA, Resolution	60
Mermel <i>et al.</i> 1989	F	29	+	Genital infection	β -lact	NA	11	Hand, Knee, Ankle, Other	NA, Persistence	730
Hannonen <i>et al.</i> 1989	M	45	+	ENT infection	β -lact	NA	8	Wrist	NA, Resolution	210
Hannonen <i>et al.</i> 1989	F	36	-	ENT infection	Linc	NA	12	Wrist, Ankle	NA, Resolution	30
Limonta <i>et al.</i> 1989	F	24	NA	ENT infection	IMDZ	NA	3	Elbow, Hand, Ankle	NA, Resolution	21
Limonta <i>et al.</i> 1989	F	25	+	Other	0	NA	8	Elbow, Hand, Ankle	NA, Resolution	28
Cope <i>et al.</i> 1992	M	48	+	Skin infection	β -lact	NA	14	Wrist, Hand, Knee, Ankle	NA, Persistence	801
Putterman <i>et al.</i> 1993	F	61	-	Digestive infection	β -lact	NA	NA	Wrist, Hand, Knee, Ankle	NA	51
Sensini <i>et al.</i> 1993	M	39	-	Prophylaxis	β -lact	NA	18	Elbow, Hand, Ankle, Foot	NA	NA
Guillemin <i>et al.</i> 1994	F	999	+	NA	NA	NA	NA	Ankle	NA	NA
Keating <i>et al.</i> 1995	M	26	+	ENT infection	β -lact	IMDZ	3	Wrist, Hand, Ankle	LCS, Resolution	43
Rochet <i>et al.</i> 1995	F	68	+	NA	β -lact	NA	0	Elbow, Knee, Ankle, Foot	NA, Resolution	8
Wright <i>et al.</i> 1996	F	36	+	ENT infection	β -lact	GLP	5	Shoulder, Wrist, Knee	0, Resolution	42
Cron <i>et al.</i> 1997	M	3	NA	ENT infection	β -lact	GLP	20	Knee	NSAID, Resolution	90
Nikkari <i>et al.</i> 1997	F	34	+	Other infection	β -lact	IMDZ	7	Wrist, Ankle	NA, Persistence	366
Löffler <i>et al.</i> 1998	F	6	-	0	0	GLP	NA	Elbow, Shoulder, Wrist, Knee	NSAID, Resolution	7
Robert <i>et al.</i> 1998	M	70	NA	ENT infection	β -lact	NA	2	Hand, Ankle, Foot	NSAID, Resolution	120
Veillard <i>et al.</i> 1998	M	57	+	ENT infection	β -lact	NA	19	Elbow, Knee, Other	NSAID + LCS, Resolution	15
Kocar <i>et al.</i> 1998	M	20	-	NA	β -lact	GLP	10	NA	NA, Resolution	27
Kocar <i>et al.</i> 1998	M	20	-	NA	β -lact	GLP	30	NA	NA	NA
Kocar <i>et al.</i> 1998	M	21	-	NA	β -lact	GLP	20	NA	NA	NA
Kocar <i>et al.</i> 1998	M	23	+	NA	β -lact	GLP	10	NA	NA, Resolution	21
Kocar <i>et al.</i> 1998	F	25	+	NA	β -lact	GLP	7	NA	NA, Resolution	25
Kocar <i>et al.</i> 1998	F	25	+	NA	0	GLP	NA	NA	NA	NA
Soderlin <i>et al.</i> 1999	F	65	+	Digestive infection	β -lact	NA	4	Ankle	NA, Resolution	330
Vermeulen <i>et al.</i> 2000	F	22	+	ENT infection	β -lact	NA	7	Shoulder, Hand, Knee	NA	NA
Vermeulen <i>et al.</i> 2000	M	67	+	Respiratory infection	Linc	NA	28	Wrist, Ankle	NA, Resolution	140
Razavi <i>et al.</i> 2000	M	47	+	Digestive infection	β -lact	IMDZ	14	Hip, Ankle, Other	NSAID, Resolution	121
Jacobs A. <i>et al.</i> 2001	F	36	+	Other infection	β -lact	IMDZ	7	Knee	0, Resolution	14
Delegue P <i>et al.</i> 2001	F	28	+	Urinary infection	β -lact	IMDZ	5	Hand, Knee, Ankle	0, Resolution	90
Löffler <i>et al.</i> 2002	M	11	+	Prophylaxis	Linc	GLP	12	Shoulder, Wrist, Ankle	NSAID, Resolution	690
Miner <i>et al.</i> 2005	M	32	NA	Digestive infection	QLN	IMDZ + GLP	7	Elbow, Knee, Foot	0, Resolution	125
Ducroix <i>et al.</i> 2006	M	45	-	Digestive infection	β -lact	IMDZ + GLP	8	Hand, Knee, Ankle, Other	NSAID, Resolution	110
Durand <i>et al.</i> 2008	F	10	NA	ENT infection	β -lact	IMDZ	30	Hip	Surgery, Resolution	20
Prati <i>et al.</i> 2008	F	64	+	Respiratory infection	β -lact	IMDZ	17	Elbow, Ankle	0, Resolution	10
Birnbaum <i>et al.</i> 2008	M	72	+	Respiratory infection	Linc	IMDZ	55	Shoulder, Knee, Ankle	NSAID + LCS, Resolution	110
Ben Abdelghani <i>et al.</i> 2009	F	43	-	0	0	IMDZ	NA	Shoulder, Wrist, Ankle	SCS, Resolution	110

Table 1: Literature review of all cases of reactive arthritis associated with *Clostridium difficile* (N=49).

Notes : - : negative, + : positive, 0 : no treatment, ATB : Antibiotic therapy, β -lact : beta-lactamin, CDI : *Clostridium difficile* infection, ENT : eye-nose-teeth, F: Female , GLP : glycopeptide, IMDZ : imidazole, LCS : local corticosteroids, Linc : lincosamide, M: male, NA : Not available, NSAID : oral non steroid anti-inflammatory drugs, QLN : quinolone, SCS : Systemic corticosteroids, TUI : time between CDI and reactive arthritis

HIGHLIGHTS

- *Clostridium difficile* associated reactive arthritis are uncommon.
- It is more likely observed in younger patients with HLA B27-positive genotype.
- Outcome was favorable in 90% of patients.

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