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**Title:**

Use of antibiotics and the prevalence of antibiotic-associated diarrhoea in patients with spinal cord injuries: an international, multicentre study.

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35 **Abstract**

36 **Background:** Little is known about the use of antibiotics and the extent of AAD in  
37 spinal cord injury (SCI) patients.

38 **Aims:** Our aim was to (1)record the use of antibiotics; (2)establish the prevalence of  
39 AAD and *Clostridium difficile* infection (CDI) and; (3)assess if there was any  
40 seasonal variation in antibiotic use and incidence of AAD.

41 **Methods:** A retrospective study was conducted in six European SCI centres during  
42 October 2014 to June 2015. We define AAD as 2 or more watery stools type 5, 6 or 7  
43 (Bristol stool scale) over 24-hours.

44 **Findings:** One-thousand-two-hundred-and-sixty-seven adults (median age: 54 years,  
45 30.7% female) with SCI (52.7% tetraplegia; 59% complete SCI) were included. Of  
46 215 (17%) patients on antibiotics, the top three indications for antibiotics were  
47 urinary-tract infections, infected pressure ulcers and other skin-infections. Thirty-two  
48 of 215 (14.9%) developed AAD and two of 1267 (0.16%) developed CDI. AAD was  
49 more common in summer season than in spring, autumn and winter.  
50 (30.3%,3.8%,7.4%,16.9%,  $p<0.01$ ). AAD was associated with adults age above 65-  
51 years, tetraplegia, higher body-mass-index, hypoalbuminaemia, polypharmacy,  
52 multiple antibiotic users and high-risk antibiotic use. The summer and winter season  
53 and male gender were identified as independent predictors for AAD.

54 **Conclusion:** This study found AAD is common in SCI patients and UTI is the most  
55 common cause of infection. Summer and winter seasons and male gender were unique  
56 predictor for AAD. Both AAD and UTI are potentially preventable, thus further work  
57 should focus on preventing the over-use of antibiotics and strategies in improving  
58 hospital infection control measures.

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62 **Keywords:** spinal cord injury centres; survey; *Clostridium difficile* infection;

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69 **Introduction**

70 Antibiotic associated diarrhoea (AAD) is a common complication of antibiotic  
71 treatment. The disturbance of normal gut microbiota, especially after antibiotic use, is  
72 thought to predispose patients to pathogenic bacterial colonisation<sup>1,2</sup> Of bacterial  
73 causes, it is reported that three predominantly opportunistic pathogens including  
74 *Clostridium difficile* (*C. diff*), *Staphylococcus aureus* and *Clostridium perfringens* are  
75 associated with AAD<sup>3</sup>. AAD is described as unexplained diarrhoea that occurs in  
76 association with antibiotic administration.<sup>3</sup> Diarrhoea is thought to be clinically  
77 significant if there are more than 3 loose stools per day<sup>4,5</sup> although a recent survey in  
78 SCI centres found the definition of diarrhoea and diagnostic criteria of *C. diff*  
79 infection (CDI) vary among spinal cord injury (SCI) centres.<sup>6</sup> In addition, diarrhoea  
80 after SCI is often complicated by spurious diarrhoea due to underlying constipation.

81

82 AAD occurs in about 5-25% of adult patients upon administration of  
83 antibiotics.<sup>4</sup> CDI occurs most often as a consequence of disruption of the gut  
84 microbiota following broad spectrum antibiotics. CDI accounts for 20-30% of AAD,  
85 although some estimates are more conservative.<sup>3,7</sup> In the majority of patients, full  
86 recovery is usual, although particularly older and frail patients may suffer loss of  
87 dignity, become seriously ill with dehydration as a consequence of the diarrhoea, and  
88 may progress to develop life threatening pseudomembranous colitis.

89

90 Exposure to antibiotics within the previous three months is thought to be one  
91 of the most important risk factors for developing CDI. Literature reported risk factors  
92 include age<sup>9,8,10</sup>, recurrent antibiotic use<sup>8,10</sup>, hospitalisation<sup>9</sup>, severity of underlying  
93 illness<sup>9</sup>, use of proton pump inhibitors (PPI)<sup>9,10,11</sup> and malnutrition<sup>12,13</sup> Seasonal  
94 variation<sup>12,14,15</sup> of CDI has been noted, however, this may not be a characteristic that  
95 is shared among all patient groups.<sup>16</sup> SCI patients are at higher risk of hospital  
96 acquired infections because of longer hospital stay for acute and rehabilitation stay.<sup>16</sup>  
97 Newly-injured SCI patients require anticoagulation therapy to prevent venous  
98 thromboembolism. This increases the risk of gastric ulcers, therefore patients  
99 commonly receive a PPI to protect the stomach against this adverse effect. Literature  
100 reports show that patients on PPIs have a relative risk of 69% of contracting *C. diff*  
101 against patients who are not taking the medication.<sup>17</sup> In addition, increased use of  
102 invasive devices such as urinary catheters increase the risks of antibiotic use, thus

103 CDIs.<sup>16,18</sup> In SCI, AAD / CDI can contribute to or complicate any pressure ulcer  
104 management as it leads to moisture and bacteria that could potentially contaminate  
105 pressure ulcers. Recurrent diarrhoea also depletes the body of electrolytes which are  
106 key in wound healing such as potassium, or during chronic episode micronutrients  
107 such as magnesium and zinc.<sup>14</sup> This is through direct loss, but also via malabsorption.  
108 Diarrhoea causes dehydration and malnutrition with further medical consequences.<sup>19</sup>

109

110 The objectives of this study were to (1) record the use of antibiotics (2)  
111 establish the prevalence of AAD and CDI and (3) assess if there is any seasonal  
112 variation in infections and prevalence of AAD in six international SCI centres.

113

#### 114 **Methods**

115 This was a one year, retrospective, point-prevalence study. The data was  
116 collected from six European SCI centres on four different dates, during the period  
117 October 2014 to June 2015. In order to analyse the seasonal variation of AAD, CDI  
118 and infections caused, we collected data from all in-patients on 4 different time  
119 points: (1) 1<sup>st</sup> October 2014 (Autumn), (2) 1<sup>st</sup> February 2015(Winter), (3) 6<sup>th</sup> April  
120 2015 (Spring), and (4) 1<sup>st</sup> June 2015 (Summer). For those SCI centre with fewer than  
121 25 beds, an additional day in each season was allocated: (1) 15<sup>th</sup> September 2014  
122 (Autumn), (2) 12<sup>th</sup> January 2015(Winter),(3) 4<sup>th</sup> March 2015(Spring), and (4) 6<sup>th</sup> July  
123 2015 (Summer).

124

125 A 30 item cross-sectional questionnaire was distributed to the SCI centres' clinicians.

126 The questionnaire consisted of three sections: the first section collected individual's  
127 baseline demographics (at the time of data collection), level and cause of SCI,  
128 presence of co-morbidities. Routine blood biochemistry and haematology data were  
129 collected +/- 3 days of study date. The second section collected the number of  
130 medications and whether patients were on antibiotics. The indication for starting  
131 antibiotics, dose, route and frequency of antibiotics, use of proton pump inhibitor, H2  
132 blocker, laxatives and anti-diarrhoeal agents were also collected. The last section was  
133 aimed at determining the occurrence of diarrhoea and *C. diff* infection.

134

135 We defined diarrhoea as 2 or more watery stools type 5, 6 or 7 (Bristol stool  
136 scale) over 24 hours.<sup>5</sup> We defined AAD as 2 or more loose stools (Bristol Stool Scale  
137 type 5,6, 7) up to 7 days after finishing antibiotics. CDI was confirmed by a positive  
138 *C. difficile* toxin A and B in stool samples.

139

140 The survey was sent to the six SCIC's medical lead in four western European  
141 countries with a covering letter addressed to the local SCI medical lead explaining  
142 that our investigation would be used to understand the use of antibiotics in their SCI  
143 centres. We aimed to include one SCIC for each country with 10 to 20 million  
144 inhabitants, and two for countries greater than 20 million inhabitants. Participating  
145 centres were reassured that all data would be treated anonymously.

146

147 Formal ethical permission to conduct the study was not required by the  
148 Institution's review board as it did not involving active patient participation.<sup>20</sup> The  
149 questionnaires were approved by the local clinical audit departments. In addition, we  
150 tested the pilot questionnaire on three patients to assess the content and time required  
151 to complete the questionnaire; feedback from this guided the drafting of the final  
152 version of the questionnaire (supplementary information). Completed questionnaires  
153 were anonymised further prior to data input and analysis. Two reminders were sent  
154 (at eight weeks and twelve weeks after the initial survey distribution).

155

156 The intensity of antibiotic exposure was used to categorise patients into those  
157 on relatively low-risk antibiotics (metronidazole and parenteral aminoglycosides),  
158 those on 'medium-risk' antibiotics (tetracyclines, sulphonamides, and macrolides) and  
159 those on 'high-risk' antibiotics (aminopenicillin, cephalosporins, lincosamides and  
160 quinolones), using the criteria described elsewhere.<sup>21</sup>

161

## 162 **Statistical analysis**

163 The prevalence of AAD and CDI was obtained by dividing the total number of  
164 patients that had developed AAD / CDI by the total number of patients studied during  
165 the study period. Descriptive statistics were used to calculate response frequency.  
166 Data was reported as mean (s.d.) or median (ranges).  $X^2$  tests were used to compare  
167 differences in the distribution of qualitative variables. Differences in quantitative

168 variables, according to their distribution, were analyzed by the parametric t test or the  
169 non-parametric Mann–Whitney test. Univariate linear regression analysis of the  
170 occurrence of AAD was then undertaken. Those which were significant ( $p < 0.05$ ) were  
171 entered into a multivariate analysis to determine which made a significant unique  
172 contribution to AAD. As only a small number of CDI occurred, multiple binary  
173 logistic regression analysis was used to determine significant predictors for AAD, and  
174 effect estimates were presented as the OR and 95% CI. For all tests, a P value of 0.05  
175 or less or when the 95% CI for OR did not exceed 1.0 was considered as significant.  
176 Statistical analysis was performed using the Minitab statistical software (version 15.0;  
177 Minitab, Inc.) and SPSS (version 19; IBM Corporation).

178

179         Approximately 35% of the routine data were missed in the present study  
180 (predominantly demographics, biochemical and hematological variables from those  
181 not on antibiotics) and approximately 10% of data were missed in those with  
182 antibiotics. To reduce the bias implicit in utilizing only complete cases, multiple  
183 imputation using SPSS (version 19; IBM Corporation, Chicago) Markov Chain Monte  
184 Carlo multiple functions were used to produce five imputed datasets. These were each  
185 analyzed as normal; thereafter, standard multiple imputation procedures were used to  
186 combine multiple scalar and multivariate estimate quantities. There was no missing  
187 data in respect of the primary end-points of the study (i.e. AAD).

188

## 189 **Results**

190         All six SCICs we approached responded to the survey. The centres contained a  
191 total of 431 SCI beds (20 in Belgium, 20 in the Netherlands, 210 in Spain and 181 in  
192 the United Kingdom. A total of 1,267 SCI (52.7% tetraplegia; 59.0% complete SCI)  
193 adults (median age: 54 years, 30.7% female) data were included in this study. No  
194 patients were excluded. 215 (17%) patients were on antibiotics; the top five  
195 indications for antibiotics were urinary tract infections ( $n=82$ , 36.7%), pressure ulcers  
196 / wound infections ( $n=45$ , 19.9%), other skin infection ( $n=17$ , 12.4%), chest infection  
197 ( $n=21$ , 9.3%) and osteomyelitis ( $n=18$ , 7.5%). (Table I) Urinary tract infections were  
198 found to be more common in the autumn season (55.6%) when compared with winter  
199 (33.9%), spring (35.7%) and summer (33.9%), respectively ( $p=0.021$ ). (Table I)

200

201 Thirty-two of 215 patients on antibiotics (14.9%) developed diarrhoea (AAD).  
202 This is significantly higher when compared to those not on antibiotics (6.4% of whom  
203 developed diarrhoea,  $p<0.01$ ). (Table II) Patients who received antibiotics tended to  
204 take more medication (13 v 10,  $p<0.01$ ), be paraplegic (57.7% v 45.1%,  $p<0.01$ ), have  
205 incomplete SCI (57.8% v 34.8%,  $p<0.01$ ), have a higher c-reactive protein (mg/L: 21  
206 v 12,  $p<0.01$ ) and be re-admissions (37.7% v 20.1%,  $p<0.01$ ). (Table II) No  
207 significant difference was found in the number of older adults, serum albumin level,  
208 body mass index, mean white cell counts, proportions of patients using proton pump  
209 inhibitor, H2 blocker, laxatives (single and multiple) and anti-diarrhoeal agents.  
210 (Table II)

211

212 The centres' antibiotic usage, percentage of antibiotic use, prevalence of AAD  
213 and CDI were varied. Table III. Overall UK SCI centres (apart from centre 5) use  
214 more antibiotics than non-UK centres (21.8% v 17%,  $p=0.035$ ). There was no  
215 statistical significant difference in the occurrence of AAD in UK and non-UK SCI  
216 patients. However, there was a statistical significant difference on the occurrence of  
217 AAD amongst UK centres (24.2%, 8.7%, 6.5%,  $p=0.036$ ) and non-UK centres (5.6%,  
218 41.2%, 0%,  $p<0.01$ ).

219

220 Overall, AAD was not significantly associated with longer duration of  
221 antibiotic therapy (mean duration, 16 days for patients with AAD vs 10 days for those  
222 without AAD,  $p=0.322$ ). (Table 3) 32.4% patients received multiple antibiotics.  
223 Patients tended to develop AAD if they were on multiple antibiotics (50% in patients  
224 with AAD vs 29.9% for those without AAD,  $p=0.041$ ). The most frequently used  
225 antibiotics regimens that were associated with AAD were piperacillin / tazobactam,  
226 clindamycin and flucoxacillin. 31.3% of patients that had developed AAD were found  
227 to be on high-risk antibiotics compared to 15.2% of patients on low-risk antibiotics,  
228  $p=0.041$ . (Table IV)

229

230 AAD was more common in the summer season when compared to spring,  
231 autumn and winter. (30.3%, 3.8%, 7.4%, 16.9%,  $p<0.01$ ). (Table. 1) AAD was  
232 associated with older adults aged 65 years or above (54.8% v 18.1%,  $p<0.01$ ),  
233 tetraplegia (68.7% v 38.2%,  $p<0.01$ ) and higher body mass index: 28.2 v 25.7,



234 p<0.01). In addition, patients with AAD tended to have a lower serum albumin level  
235 (28g/L v 34g/L, p<0.001), receive more medications (14 v 11, p<0.01), H<sub>2</sub> blocker  
236 user (21.9% v 5.4%, p<0.01), multiple antibiotics (50% v 29.9%, p=0.041) and use  
237 high-risk antibiotics (31.4% v 15.2%, p=0.041).

238

239 The binary multivariate logistic regression analysis identified summer season  
240 (OR 7.77, 95% CI 1.49, 40.7), winter season (OR 6.0, 95% CI 1.1, 33.7), adult age  
241 greater than 65 years old (OR 3.22, 95% CI 1.27, 8.18) and being male (OR: 5.34, 95%  
242 CI 1.2, 23.7) as the unique risk factors for AAD. (Table V)

243

244 As only a small number of patients developed CDI (n=2), this form of analysis  
245 was deemed inappropriate for the CDI data.

246

## 247 **Discussion**

248 The purpose of this study was to establish the prevalence and assess whether seasonal  
249 variation affects the occurrence of AAD and CDI among SCI patients. The prevalence  
250 of AAD was 14.9% and CDI was 0.24%. This is comparable with the reported  
251 prevalence of AAD<sup>3</sup> and CDI<sup>7</sup> in general populations and previous studies conducted  
252 in SCI centres.<sup>19,22</sup> Our study found that summer and winter seasons and male gender  
253 are unique risk factors for AAD.

254

255 The prevalence of AAD varied between SCI centres, this could be due to non-  
256 standardised infection prevention and control and antimicrobial stewardship  
257 practices<sup>6</sup>. In addition some SCI centres may have a different threshold for use of  
258 antibiotics as they may be part of general hospitals which have Trauma centres and /  
259 or Emergency Departments (therefore a higher chance of prescribing antibiotics after  
260 trauma and spinal surgery) when compared to some centres just admitting elective  
261 admissions from other general hospitals.

262

263 Antibiotic administration causes an alternation in intestinal microbiota, which  
264 results in the loss of physiologic processes involving the metabolism of nutrients.  
265 Multiple antibiotics have been implicated in reduced colonic bacterial carbohydrate  
266 metabolism. Clindamycin has been shown in vitro to decrease faecal carbohydrate  
267 metabolism as well as concentrations of SCFA. Our data found that a significant

268 higher proportion of patients that developed AAD were on higher-risk antibiotics and  
269 this is comparable to previous reports.<sup>21</sup>

270

271 The present study found the prevalence of CDI was low in comparison to  
272 previous reports.<sup>13,14,15</sup> The fall in CDI prevalence reflects the continuing year-on-  
273 year fall of overall *Clostridium difficile* infection cases in British hospitals. Indeed,  
274 the overall CDI rate for England in the UK has fallen from 148.7 cases per 100,000 in  
275 2007/8 to 40.8 per 100,000 in 2015/6.<sup>24</sup> In addition, the low prevalence of CDI could  
276 be due to the variation in AAD and CDI definition amongst SCI centres<sup>25</sup>, short study  
277 time period and point prevalence nature of the study. However, the surprisingly low  
278 CDI in our European centres (0% in all 3 centres) may be due to being under-  
279 diagnosed as they lack established CDI surveillance systems.<sup>26</sup>

280

281 Due to the limited number of CDI cases (n=2) in the present study, we were  
282 not able to analyse potential risk factors for CDI but, apart from the traditional risk  
283 factors, our study found summer season and polypharmacy may be additional risk  
284 factors for AAD.

285

#### 286 Strengths and limitations

287 The main strength of this study is that it is the first official international study  
288 conducted in a multicenter European setting which has a large sample size (n=1,267).  
289 It also includes a mixture of various sized centres from both centres admitting elective  
290 and emergency patients immediately after SCI, therefore this study allows inter-centre  
291 comparison.

292

293 This study has some limitations. Firstly, some large centres may be over-  
294 represented in the results. To tackle this, we instructed an additional data collection  
295 date for centres having fewer than 25 beds. Secondly, the present study did not judge  
296 whether the use of antibiotics was appropriately prescribed, therefore it may  
297 overestimate the use of antibiotics especially in centres without established antibiotic  
298 stewardship. The selection of the SCIC was at the discretion of the study authors,  
299 however, the SCI centres represented approximately 15-20% of the SCIC's beds in the  
300 UK, Belgium, the Netherlands and Spain. Therefore, results derived from this sample

301 of SCICs could be considered representative. Thirdly, we defined the follow up period as  
302 7-days after their initial course of antibiotics is finished. However, we acknowledge that  
303 AAD/ CDI may occur up to three months after the initial exposure of antibiotics.<sup>27</sup> In order to  
304 assess the risk factor of AAD / CDI in SCI patients, we recommended a further study to  
305 include the history of antibiotic use in the previous three months and a longer follow up  
306 period is warranted. Finally, different SCI centres may have different policies on  
307 antibiotic prescribing and different catheter and bowel management programmes.  
308 Previous research has found different definitions of diarrhoea have been used in  
309 different SCICs in the UK and other European SCI centres.<sup>6</sup> Indeed, to use a  
310 standardised definition of diarrhoea would not just help in identifying and treating  
311 patients with diarrhoea but also allowing bench-marking with other SCI centres to  
312 strengthen future AAD / CDI research.

313

#### 314 **Conclusions**

315 Our study indicates CDI is a relatively uncommon occurrence in SCI patients, despite  
316 antibiotic use being relatively common in SCI patients, and diarrhoea being associated  
317 with antibiotic use. UTI is the most common cause of infection in this group of  
318 patients and efforts to prevent this will significantly reduce the numbers of antibiotic  
319 courses prescribed. Further studies should focus on whether AAD is associated with  
320 adverse clinical outcomes such as longer hospital stay and/or prolonged rehabilitation.  
321 As both UTI and AAD are potentially preventable, additional focus on implementing  
322 standardized infection control practice / surveillance systems across SCI centres and  
323 improving antimicrobial stewardship could reduce the incidence of UTI and AAD,  
324 especially in summer and winter seasons.

325

#### 326 **Contributions**

327 SW- Protocol development, Questionnaire development, data analysis, manuscript  
328 preparation

329 PS – data collection, data input, manuscript revision

330 SH- data analysis, data interpretation, manuscript revision

331 NK – data collection, manuscript revision

332 JRC – data collection, manuscript revision

333 AGF – data collection, data interpretation, manuscript revision  
334 MR – data collection, manuscript revision  
335 FP – data collection, manuscript revision  
336 IZ – data collection, data input, manuscript revision  
337 SK – data interpretation, manuscript revision  
338 CK – data collection, data interpretation, manuscript revision  
339 ND – data collection, data interpretation, manuscript revision  
340 ER – data collection, data interpretation, manuscript revision  
341 JMB – data collection, manuscript revision  
342 JO'D- data interpretation, manuscript revision  
343 AJ- data interpretation, manuscript revision  
344 MS – questionnaire development, data interpretation, manuscript revision

345

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350 collection and Janine Turner for proof-reading the manuscript

351

352 **Conflict of interest:** Parts of the study data were submitted to present at the BritSpine  
353 in April 2016, American Spinal Injury Association annual conference in April 2016 ,  
354 International Spinal Cord Society meeting in September 2016 and FIS / HIS  
355 conference in November 2016.

356

357 **Source of funding:** none.

358

359 **Table I. Summary of infections in SCICs by seasons**

360		<b>All</b>	<b>Spring</b>	<b>Summer</b>	<b>Autumn</b>	<b>Winter</b>	<b>P-value</b>
361	Total no. of patients	1267	n=345	n=355	n=342	n=338	
362	Urinary tract infection*	82, 36.7%	15, 35.7%	19, 33.9%	30, 55.6%	18, 33.9%	0.021
363	Pressure ulcers / wound infection	45, 19.9%	15, 28.8%	11, 19.6%	9, 16.7%	10, 18.9%	0.431
364	Skin infection	17, 12.4%	6, 11.5%	4, 7.1%	3, 5.6%	4, 7.5%	0.704
365	Chest infection	21, 9.3%	3, 5.8%	6, 10.7%	7, 12.9%	5, 9.4%	0.652
366	Osteomyelitis	18, 7.5%	6, 11.5%	7, 12.5%	2, 3.7%	3, 5.7%	0.265
367	Spinal metal work infection	11, 4.9%	2, 3.8%	5, 8.9%	1, 1.9%	3, 5.7%	0.381
368	Gall bladder infection	7, 3.1%	2, 3.8%	0, 0%	0, 0%	5, 9.4%	-
369	Infected cysts	4, 1.8%	1, 1.9%	0, 0%	1, 1.9%	2, 3.8%	-
370	Eye infection	3, 1.3%	2, 3.8%	1, 1.8%	0, 0%	0, 0%	-
371	Nail infection	2, 0.9%	0, 0%	2, 3.6%	0, 0%	0, 0%	-
372	Sepsis	2, 0.9%	0, 0%	1, 1.8%	0, 0%	1, 1.9%	-
373	Ear infection	1, 0.4%	0, 0%	0, 0%	0, 0%	1, 1.9%	-
374	Spinal TB	2, 0.9%	0, 0%	0, 0%	1, 1.9%	1, 1.9%	-
375	Total no. of infections	215, 17.8%	52, 15.1%	56, 16.7%	54, 15.8%	53, 15.7%	0.992
376							
377	AAD †	32, 14.9%	2, 3.8%	17, 30.3%	4, 7.4%	9, 16.9%	p<0.01
378	CDAD	4, 0.24%	0, 0%	0, 0%	1, 0.3%	1, 0.3%	-

379

380 \* p <0.05; † p<0.01; AAD: antibiotic associated diarrhoea; CDAD: *Clostridium difficile* associated diarrhoea; \*\*\* Less than 5 case, no statistic test performed

381 \*\* n=37 patients were prescribed antibiotic as prophylaxis; some data inconsistent / change e.g. nail infection was due to f/u review to confirm indication of infection.

382 Table II Baseline characteristics of the study participants (Number of patients and percentages or median values)

383		Overall	On antibiotics	Not on antibiotics	P-value
384	Parameters				
385	No. of diarrhoea†	61 out of 685 (8.9%)	32 out of 215 (14.9%)	29 out of 448 (6.4%)	<0.001
386	No. of C. diff infection	4 out of 685 (0.6%)	1 out of 237 (1.3%)	3 out of 448 (0.7%)	ns
387	Median no. of drugs†	10 (range: 1-28)	13	10	<0.001
388	No. of patient > 65 years	176 out of 685 (25.6%)	54 out of 234 (23.1%)	122 out of 448 (27.2%)	0.269
389	Median age	54 (range: 18-91)	59	55	0.871
390	No. of cervical SCI†	344 out of 680 (50.5%)	100 out of 236 (42.3%)	244 out of 444 (54.9%)	0.002
391	No. of complete SCI (AIS: A) †	386 out of 673 (57.4%)	97 out of 230 (42.2%)	289 out of 443 (65.2%)	<0.001
392	Median body mass index (Kg/m <sup>2</sup> )	28.9	26.6	25	0.060
393	No. of overweight (BMI>25 kg/m <sup>2</sup> )	239 out of 456(52.4%)	70 out of 121 (57.9%)	169 out of 335 (50.4%)	0.169
394	Median of albumin (g/L) *	34	33	34	0.435
395	Median C-reactive protein (mg/L) †	13	21	12	<0.001
396	Median white cell counts (10 <sup>9</sup> /L)	7.2	7.6	7.5	0.734
397	No. of proton pump inhibitor*	342 out of 620 (55.1%)	144 out of 236 (61.0%)	198 out of 384 (51.5%)	0.025
398	No. of H <sub>2</sub> blocker	56 out of 612 (9.2%)	18 out of 234 (7.7%)	38 out of 378 (10.1%)	0.387
399	No. of patient on laxatives	539 out of 618 (87.2%)	198 out of 235 (84.3%)	341 out of 383 (89.0%)	0.106
400	No. of multiple laxatives	409 out of 539 (75.8%)	142 out of 198(71.7%)	267 out of 341 (78.3%)	0.077
401	No. of anti-diarrhoeal agents	9 out of 602 (1.5%)	6 out of 227 (2.6%)	3 out of 375 (0.8%)	0.088
402	No. of new admission†	504 out of 683 (73.7%)	147 out of 236 (62.3%)	357 out of 447 (79.9%)	<.0001

403 AAD: antibiotic associated diarrhoea; GDH: glutamate dehydrogenase; CDAD: clostridium difficile associated diarrhoea; IV: intravenous; SCI: spinal cord injury; AIS: American Spinal Injury  
 404 Association Impairment Scale  
 405

407 ^^ We only reported available / returned case, especially for those not-on antibiotics

408 \* p <0.05; † p<0.01

409 Table III Centre's antibiotic usage, prevalence of antibiotic associated diarrhoea (AAD) and *Clostridium difficile* associated diarrhoea (CDAD)  
 410

Centre	No. of patients	No. of antibiotics	% of antibiotics	No. of AAD (%)	CDAD
<b>UK centre 1</b>	261	70	26.8	17/70, 24.2%	1/70, 1.4%
<b>UK centre 2</b>	177	23	12.9	2/23, 8.7%	0/23
<b>UK centre 3</b>	129	31	24	2/31, 6.5%	0/31
<b>Non-UK centre 4</b>	571	90	15.8%	5/90, 5.6%	0/90
<b>Non-UK centre 5</b>	49	17	34.7	7/17, 41.2%	0/17
<b>Non-UK centre 6</b>	45	6	13.3	0/6	0/6
<b>UK total</b>	567	124	21.8	21/124, 16.9%	1/124, 0.81%
<b>Non-UK total</b>	665	113	17.0	12/ 113, 10.6%	0/113, 0%
<b>Overall</b>	1232	237	19.2	33/237, 13.9%	1/237, 0.42%

- 411  
 412 1. UK SCI patients seems to receive more antibiotic than in non-UK SCI patients. 21.8% v 17%, p=0.0353  
 413 2. No statistical significant difference between the occurrence of AAD in UK and non-UK population.  
 414 3. There is a statistical significant difference between UK centres in occurrence of AAD, 24.2% v 8.7% v 6.5%, p=0.036  
 415 4. There is a statistical significant difference between non-UK centres in AAD, 5.6% v 41.2% v 0%, p<0.001

416 Table IV Baseline characteristics of the study participants on antibiotics (Number of patients and percentages or median values)

417		Developed AAD	Did not developed AAD	P-value
418				
419	Parameters			
420	No. of patient > 65 years†	17 out of 31 (54.8%)	37 out of 204 (18.1%)	<0.01
421	No. of cervical SCI†	22 out of 32 (68.7%)	78 out of 204 (38.2%)	<0.01
422	No. of complete SCI (AIS: A)	21 out of 32 (65.6%)	113 out of 199 (56.8%)	0.441
423	Median body mass index (Kg/m <sup>2</sup> ) †	28.8	25.7	<0.01
424	Median serum albumin (g/L) †	28	34.0	<0.01
425	No. of hypoalbuminaemia (<30g/L)*	14 out of 26 (53.8%)	49 out of 181 (27.1%)	0.011
426	No. of drugs†	14	11	<0.01
427	No. of proton pump inhibitor	15 out of 32 (46.9%)	129 out of 204 (63.2%)	0.083
428	No. of H <sub>2</sub> blocker †	7 out of 32 (21.9%)	11 out of 202 (5.4%)	<0.01
429	No. of patient on laxatives	25 out of 32 (78.1%)	173 out of 203 (85.2%)	0.302
430	No. of multiple laxatives	17 out of 25 (68.0%)	125 out of 173 (72.3%)	0.641
431	No. of anti-diarrhoeal agents	2 out of 31 (6.5%)	4 out of 196 (2%)	0.191
432	No. of new admission	17 out of 32 (53.1%)	130 out of 204 (63.7%)	0.327
433	Median onset of SCI (days)	501	365	0.267
434	Duration of antibiotics	16	10	0.322
435	No. of multiple antibiotics *	16 out of 32 (50.0%)	61 out of 204 (29.9%)	0.041
436	No. of high-risk antibiotics †	15 out of 32 (46.9%)	48 out of 204 (23.5%)	<0.01
437				
438	AAD: antibiotic associated diarrhoea; CDAD: clostridium difficile associated diarrhoea; IV: intravenous; SCI: spinal cord injury; AIS: American Spinal Injury Association Impairment Scale			
439	* p <0.05; † p<0.01			



440 Table V. Multivariate logistic regression analysis to identify risk factors for antibiotics associated diarrhoea  
 441 (Standard errors, odds ratios and 95% confidence intervals)

444	<b>Variable</b>	<b>SE</b>	<b>OR</b>	<b>95% CI</b>	<b>p-value</b>
446	Seasons (spring reference)				
448	Summer	0.844	7.77	1.49, 40.7	0.015
449	Autumn	0.961	1.84	0.28, 12.1	0.525
450	Winter	0.881	6.00	1.07, 33.7	0.042
452	Female gender	0.775	0.18	0.04, 0.81	0.026
454	Age >65 years old	0.475	3.22	1.27, 8.17	0.014
456	No. of antibiotics	0.325	1.23	0.65, 2.31	0.535
458	No. of drug	0.051	1.09	0.99, 1.21	0.070
460	Tetraplegia	0.469	0.48	0.19, 1.21	0.120
462	Use of H <sub>2</sub> blocker	0.639	0.33	0.09, 1.15	0.083

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