Title:

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

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Abstract

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

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

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

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

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

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

Introduction

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

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

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

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

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

Methods

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

A 30 item cross-sectional questionnaire was distributed to the SCI centres' clinicians. The questionnaire consisted of three sections: the first section collected individual's baseline demographics (at the time of data collection), level and cause of SCI, presence of co-morbidities. Routine blood biochemistry and haematology data were collected +/- 3 days of study date. The second section collected the number of medications and whether patients were on antibiotics. The indication for starting antibiotics, dose, route and frequency of antibiotics, use of proton pump inhibitor, H2 blocker, laxatives and anti-diarrhoeal agents were also collected. The last section was aimed at determining the occurrence of diarrhoea and *C. diff* infection.

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

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

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

The intensity of antibiotic exposure was used to categorise patients into those on relatively low-risk antibiotics (metronidazole and parenteral aminoglycosides), those on 'medium-risk'antibiotics (tetracyclines, sulphonamides, and macrolides) and those on 'high-risk' antibiotics (aminopenicillin, cephalosporins, lincosamides and quinolones), using the criteria described elsewhere.[21]

Statistical analysis

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

variables, according to their distribution, were analyzed by the parametric t test or the non-parametric Mann–Whitney test. Univariate linear regression analysis of the occurrence of AAD was then undertaken. Those which were significant ($p<0.05$) were entered into a multivariate analysis to determine which made a significant unique contribution to AAD. As only a small number of CDI occurred, multiple binary logistic regression analysis was used to determine significant predictors for AAD, and effect estimates were presented as the OR and 95% CI. For all tests, a P value of 0·05 or less or when the 95% CI for OR did not exceed 1·0 was considered as significant. Statistical analysis was performed using the Minitab statistical software (version 15.0; Minitab, Inc.) and SPSS (version 19; IBM Corporation).

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

Results

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

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

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

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

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

p<0.01). In addition, patients with AAD tended to have a lower serum albumin level (28g/L v 34g/L, p<0.001), receive more medications (14 v 11, p<0.01), H_2 blocker user (21.9% v 5.4%, p<0.01), multiple antibiotics (50% v 29.9%, p=0.041) and use high-risk antibiotics (31.4% v 15.2%, p=0.041).

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

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

Discussion

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

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

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

higher proportion of patients that developed AAD were on higher-risk antibiotics and this is comparable to previous reports.[21]

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

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

Strengths and limitations

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

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

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

Conclusions

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

Contributions

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

PS – data collection, data input, manuscript revision

SH- data analysis, data interpretation, manuscript revision

NK – data collection, manuscript revision

JRC – data collection, manuscript revision

AGF – data collection, data interpretation, manuscript revision

MR – data collection, manuscript revision

FP – data collection, manuscript revision

IZ – data collection, data input, manuscript revision

SK – data interpretation, manuscript revision

CK – data collection, data interpretation, manuscript revision

ND – data collection, data interpretation, manuscript revision

ER – data collection, data interpretation, manuscript revision

JMB – data collection, manuscript revision

JO'D- data interpretation, manuscript revision

AJ- data interpretation, manuscript revision

MS – questionnaire development, data interpretation, manuscript revision

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

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Table I. Summary of infections in SCICs by seasons

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

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

** 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.

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

Parameters	Overall	On antibiotics	Not on antibiotics	P-value
No. of diarrhoea†	61 out of 685 (8.9%)	32 out of 215 (14.9%)	29 out of 448 (6.4%)	<0.001
No. of C. diff infection	4 out of 685 (0.6%)	1 out of 237 (1.3%)	3 out of 448 (0.7%)	ns
Median no. of drugs†	10 (range: 1-28)	13	10	<0.001
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
Median age	54 (range: 18-91)	59	55	0.871
No. of cervical SCI†	344 out of 680 (50.5%)	100 out of 236 (42.3%)	244 out of 444 (54.9%)	0.002
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
Median body mass index (Kg/m^2)	28.9	26.6	25	0.060
No. of overweight (BMI>25 kg/m^2)	239 out of 456(52.4%)	70 out of 121 (57.9%)	169 out of 335 (50.4%)	0.169
Median of albumin (g/L) *	34	33	34	0.435
Median C-reactive protein (mg/L) †	13	21	12	<0.001
Median white cell counts ($10^9/L$)	7.2	7.6	7.5	0.734
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
No. of H_2 blocker	56 out of 612 (9.2%)	18 out of 234 (7.7%)	38 out of 378 (10.1%)	0.387
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
No. of multiple laxatives	409 out of 539 (75.8%)	142 out of 198(71.7%)	267 out of 341 (78.3%)	0.077
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
No. of new admission†	504 out of 683 (73.7%)	147 out of 236 (62.3%)	357 out of 447 (79.9%)	<.0001

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

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

* $p < 0.05$; † $p < 0.01$

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

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

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

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

	Developed AAD	Did not developed AAD	P-value
Parameters			
No. of patient > 65 years†	17 out of 31 (54.8%)	37 out of 204 (18.1%)	<0.01
No. of cervical SCI†	22 out of 32 (68.7%)	78 out of 204 (38.2%)	<0.01
No. of complete SCI (AIS: A)	21 out of 32 (65.6%)	113 out of 199 (56.8%)	0.441
Median body mass index (Kg/m^2) †	28.8	25.7	<0.01
Median serum albumin (g/L) †	28	34.0	<0.01
No. of hypoalbuminaemia (<30g/L)*	14 out of 26 (53.8%)	49 out of 181 (27.1%)	0.011
No. of drugs†	14	11	<0.01
No. of proton pump inhibitor	15 out of 32 (46.9%)	129 out of 204 (63.2%)	0.083
No. of H_2 blocker †	7 out of 32 (21.9%)	11 out of 202 (5.4%)	<0.01
No. of patient on laxatives	25 out of 32 (78.1%)	173 out of 203 (85.2%)	0.302
No. of multiple laxatives	17 out of 25 (68.0%)	125 out of 173 (72.3%)	0.641
No. of anti-diarrhoeal agents	2 out of 31 (6.5%)	4 out of 196 (2%)	0.191
No. of new admission	17 out of 32 (53.1%)	130 out of 204 (63.7%)	0.327
Median onset of SCI (days)	501	365	0.267
Duration of antibiotics	16	10	0.322
No. of multiple antibiotics *	16 out of 32 (50.0%)	61 out of 204 (29.9%)	0.041
No. of high-risk antibiotics †	15 out of 32 (46.9%)	48 out of 204 (23.5%)	<0.01

AAD: antibiotic associated diarrhoea; CDAD: clostridium difficile associated diarrhoea; IV: intravenous; SCI: spinal cord injury; AIS: American Spinal Injury Association Impairment Scale

* p <0.05; † p<0.01

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

Variable	**SE**	**OR**	**95% CI**	**p-value**
Seasons (spring reference)				
Summer	0.844	7.77	1.49, 40.7	0.015
Autumn	0.961	1.84	0.28, 12.1	0.525
Winter	0.881	6.00	1.07, 33.7	0.042
Female gender	0.775	0.18	0.04, 0.81	0.026
Age >65 years old	0.475	3.22	1.27, 8.17	0.014
No. of antibiotics	0.325	1.23	0.65, 2.31	0.535
No. of drug	0.051	1.09	0.99, 1.21	0.070
Tetraplegia	0.469	0.48	0.19, 1.21	0.120
Use of H_2 blocker	0.639	0.33	0.09, 1.15	0.083

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