Title:

Use of antibiotic and prevalence of antibiotic-associated diarrhoea in patients with spinal cord injuries: a UK National Spinal Injury Centre experience

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Abstract

Introduction: The frequency of antibiotic-associated diarrhoea (AAD) could be as high as 60% during hospital outbreaks. Little is known about the use of antibiotics and the extent of AAD in spinal cord injury (SCI) patients. Our aim was to (1) record the use of antibiotics; (2) establish the prevalence of AAD and *Clostridium difficile* associated diarrhoea (CDAD) and; (3) assess if there was any seasonal variation in antibiotic use and incidence of AAD.

Methods: A retrospective audit was conducted in a British SCI centre during October 2014 to June 2015. Data was collected using a standardised questionnaire. We define AAD as 2 or more watery stools type 5, 6 or 7 (Bristol stool scale) over 24 hours.

Results: Three-hundred-and-nineteen adults (mean age: 55.9 years, 29.2% female) with SCI (58.2% tetraplegia; 43.7% complete SCI) were included. Of 70 (21.9%) patients on antibiotics, the top three indications for antibiotics were urinary-tract infections, infected pressure ulcers and other skin-infections. Seventeen of 78 (21.8%) developed AAD and three of 319 (0.94%) developed CDAD. AAD was more common in the summer season than in spring, autumn and winter. (47.1%, 10.0%, 10.0%, 23.8%, p=0.025). AAD was associated with older adults greater than 65 years. (70.6% v 23.8%, p=0.007) Polypharmacy and the summer season were identified as independent predictors for AAD.

Conclusion: This survey found AAD is common in SCI patients and may be a risk factor for a poorer outcome and increased hospital costs. A multicenter study is underway to establish the incidence and risk factors for AAD.

Keywords: spinal cord injury centres; probiotics; survey; *Clostridium difficile*; antibiotic-associated diarrhoea

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] It is reported that three predominantly opportunistic pathogens including *Clostridium difficile (C. diff), Staphylococcus aureus* and *Clostridium perfringens* were 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] *C. diff* associated diarrhoea (CDAD) occurs most often as a consequence of disruption of the gut microbiota following a broad-spectrum of antibiotic treatment. CDAD 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 elderly 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 CDAD. Other well-recognised risk factors include age[9], hospitalisation[9], severity of underlying illness[9], use of proton pump inhibitors[9], malnutrition risk[10] and seasonal variation.[11] However, this may not be a characteristic that is shared among all patient groups.[12] SCI patients are at higher risk of hospital acquired infections because of longer hospital stay for acute and rehabilitation stay.[12] Newly-injured SCI patients require anticoagulation therapy to prevent venous thromboembolism. This increases the risk of gastric ulcers, therefore patients commonly receive a proton pump inhibitor (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.[13] In addition, increased use of invasive devices such as urinary catheters increases the risks of infections. [12] AAD / CDAD can complicate any pressure ulcer management as it contributes moisture and bacteria. 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.[15]

The objective of this study was to (1) record the use of antibiotics; (2) establish the prevalence of AAD and CDAD and; (3) assess if there is any seasonal variation on infections and prevalence of AAD in a UK leading SCI centre.

Methods

This was a one year, retrospective, point-prevalence study. The data was collected from the National Spinal Injuries Centre at Stoke Mandeville Hospital, UK during October 2014 to June 2015. A 30 item cross-sectional questionnaire was distributed to the SCI centre's clinicians. The questionnaire consisted of three sections: the first section was collecting individual's baseline demographics, level and cause of SCI, presence of co-morbidities and routine blood biochemistry. The second section was collecting the number of medications and whether patients are 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 occurrence of diarrhoea and *C. diff* infection.

We define AAD as 2 or more watery stools type 5, 6 or 7 (Bristol stool scale) over 24 hours.[5] CDAD was diagnosed by a positive *C. difficile* toxin A and B in stool samples.

Formal ethical permission to conduct the study was not required by the Institution's review board as this was considered to be a clinical audit not involving active patient participation.[16] 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 prior to data input and analysis.

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, macrolides and quinolones) and those on 'high-risk' antibiotics (aminopenicillin and cephalosporins), using the criteria described elsewhere.[17]

In order to analyse the seasonal variation of AAD, CDAD and infections caused, we collected data from all in-patients from 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.

Statistical analysis

The prevalence of AAD and CDAD was obtained by dividing the total number of patients that had developed AAD / CDAD 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 analysed 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 CDAD, 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).

Results

A total of 319 adults (mean age: 55.9 years, 29.2% female) with SCI (58.2% tetraplegia; 43.7% complete SCI) were studied. Seventy (24.3%) patients were on antibiotics, the top five indications for antibiotics were urinary-tract infections (n=16, 20.5%), pressure ulcers / wound infections (n=12, 15.6%), skin-infection (n=12, 15.6%), nail infection (n=8, 10.4%) and osteomyelitis (n=7, 9.1%). (Table 1) Urinary tract infections were found to be more common in the autumn season (50%) when compared with winter (14.3%), spring (5%) and summer (11.8%), respectively ($p<0.001$). (Table 1)

Seventeen of 78 patients on antibiotics (21.8%) developed diarrhoea (AAD). This is significantly higher when compared to those not on antibiotics (5.8%). (Table 2) Patients who received antibiotics tended to take more medications (13 v 10, $p<0.01$) and had a higher c-reactive protein (18 v 8.1, $p<0.001$). (Table 2) No significant difference was found in the number of older adults, severity of SCI (number of cervical injury and number of complete SCI), serum albumin level, mean white cell counts, proportions of patients using proton pump inhibitor, H2 blocker, laxatives and anti-diarrhoeal agents. (Table 2)

AAD was not significantly associated with longer duration of antibiotic therapy (mean duration, 16 days for patients with AAD vs 14 days for those without AAD, p= 0.610). (Table 3) 44.2% patients received multiple antibiotics. Patients tended to develop AAD if they were on multiple antibiotics (70.6% in patients with AAD vs 35.8% for those without AAD, p=0.023). The most frequently used antibiotics regimen that were associated with AAD were tazocin, clindamycin and flucoxacillin. 52.9% of patients that had developed AAD were found to be on high-risk antibiotics compared to 37.7% of patients on low-risk antibiotics, p=0.397. (Table 3)

AAD was more common in the summer season when compared to spring, autumn and winter. (47.1%, 10%, 10%, 23.8%, p=0.025). (Table. 1) AAD was associated with older adults aged 65 years or above (70.6% v 31%, p=0.003) and tetraplegia (76.5% v 44.4%, p=0.021). In addition, patients with AAD tended to have a lower serum albumin level (24.5g/L v 31.5g/L, $p<0.001$).

The binary multivariate logistic regression analysis identified the polypharmacy (OR 1.17, 95% CI 1.00, 1.37) and summer season (OR 14.45, 95% CI 1.17, 178.1) as the unique risk factor for AAD. (Table 4)

As only a small number of patients developed CDAD (n=3), this form of analysis was deemed inappropriate for the CDAD data.

Discussion

The purpose of this study was to establish the prevalence and assess whether seasonal variation affects the occurrence of AAD and CDAD among SCI patients. The prevalence of AAD was 22.1% and CDAD was 1.3%. This is comparable with the reported prevalence of AAD[3] and CDAD[7] in general populations and previous studies conducted in SCI centres.[15] Our study found that summer season and polypharmacy are unique predictors for AAD.

Antibiotic administration causes alternation in intestinal microbiota, which results in the loss of physiologic processes involving the metabolism of nutrients. Under normal circumstances, non-absorbable carbohydrates are metabolized by anaerobic colonic bacteria as an energy source. As metabolism occurs, lactic acid and short-chain fatty acids (SCFAs) such as butyrate are produced. Fluid, electrolytes, and SCFAs are absorbed, with only small amounts of these organic acids remaining in the colon. Undigested non-absorbable carbohydrates, organic acids and cations accumulate, causing osmotic diarrhoea. 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. Ampicillin, metronidazole, dicloxacillin, and erythromycin have also been implicated in causing reduced faecal concentrations of SCFA.[18] Our data found a higher proportion of patients that developed AAD were on higher-risk antibiotics but we failed to find any statistical association.

Another pathway that could be significantly affected by antibiotic administration involves the synthesis of primary bile salts. If bile salts are not absorbed in the small bowel, bile salts will dehydroxylated to secondary bile acids by bacteria in the colon. These secondary bile acids are potent colonic secretory agents, and presence in the colon can cause secretory diarrhoea. In addition, the increase in colonic pH caused by decreased carbohydrate metabolism results in increased solubility of dehydroxylated secondary bile salts, so these mechanisms may actually work in synergy to cause AAD.[18]

The present study found the prevalence of CDAD was low in comparison to previous reports. [6,10,11] The fall in CDAD prevalence could be due to 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 4.85 per 10,000 in 2009 to 2.29 per 10,000 in 2013.[19] In addition, the low prevalence of CDAD could be due to short study time period and point prevalence nature of the study.

Risk factors associated with CDI have been investigated in many studies. Prior antimicrobial use is a well known risk factor for developing CDI. Antimicrobials alter the healthy faecal microbiome, allowing *C. diff* to colonise, overgrow, and produce toxins if a *C. diff* exposure occurs before the faecal microbiome is able to return to a healthy state. Traditionally, clindamycin has been associated with CDI, and it remains an important predisposing risk factor today.[20] Exposure to gastric acid suppressive agents has also been identified as a risk factor associated with CDI.[21] The mechanism of action of gastric acid suppression in the causal pathway of CDI is not fully known. As an obligate anaerobe, the vegetative cells of *C. diff* die within minutes after exposure to air. Therefore, *C. diff* acquisition involves the ingestion of C. diff spores, which are resistant to gastric acid. Rather than being in the causal pathway of CDI, gastric acid suppression may be a surrogate marker for patients at increased risk of CDI.[22] Due to limited case in the present study, we were not able to analyse potential risk factors for CDAD but, apart from the traditional risk factors, our study found summer season and polypharmacy may be additional risk factors for AAD.

This study has some limitations. Firstly, the present study did not judge whether the use of antibiotic was appropriate therefore it may overestimate the use of antibiotic. The selection of the SCIC was at discretion of the study authors. However, the SCI centre (National Spinal Injuries Centre at Stoke Mandeville Hospital) selected is the largest SCI centre (115 beds) in the UK and represented approximately 25% of the SCIC's beds in the UK. Therefore, results derived from this sample of SCICs could be considered representative or at least serve as a pilot study. To include one large SCIC may prevent the differences on antibiotic prescription and bowel management programme between SCICs. 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 SCI but also allowing bench marking with other SCI centres and to enable future AAD / CDAD research.

Conclusions

The present study found AAD is common in SCI patients and may be a risk factor for poorer outcome and increased hospital cost. A multicenter study is planned to establish the prevalence and risk factors for AAD / CDAD.

Supplementary information is available on the Journal's website

Contributions

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

PS – data input, manuscript revision

JO'D- data interpretation, manuscript revision

SH- data analysis, 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 and International Spinal Cord Society meeting in September 2016.

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