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

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SUMMARY

Background: Little is known about the use of antibiotics and the extent of antibiotic-associated diarrhoea (AAD) in patients with spinal cord injuries (SCIs).

Aims: To record the use of antibiotics, establish the prevalence of AAD and *Clostridium difficile* infection (CDI), and assess if there was any seasonal variation in antibiotic use and incidence of AAD in patients with SCIs.

Methods: A retrospective study was conducted in six European SCI centres between October 2014 and June 2015. AAD was defined as two or more watery stools (Bristol Stool Scale type 5, 6 or 7) over 24 h.

Findings: In total, 1267 adults (median age 54 years, 30.7% female) with SCIs (52.7% tetraplegia, 59% complete SCI) were included in this study. Among the 215 (17%) patients on antibiotics, the top three indications for antibiotics were urinary tract infections (UTIs), infected pressure ulcers and other skin infections. Thirty-two of these 215 (14.9%) patients developed AAD and two patients out of the total study population (2/1267; 0.16%) developed CDI. AAD was more common in summer than in spring, autumn or winter (30.3% vs 3.8%, 7.4% and 16.9%, respectively; $P<0.01$). AAD was associated with age ≥65 years, tetraplegia, higher body mass index, hypoalbuminaemia, polypharmacy, multiple

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antibiotic use and high-risk antibiotic use. Summer and winter seasons and male sex were identified as independent predictors for the development of AAD.

Conclusion: This survey found that AAD is common in patients with SCIs, and UTI is the most common cause of infection. Summer and winter seasons and male sex are unique predictors for AAD. Both AAD and UTIs are potentially preventable; therefore, further work should focus on preventing the over-use of antibiotics, and developing strategies to improve hospital infection control measures.

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 colonization [1,2]. Of the bacterial causes, it is reported that three predominantly opportunistic pathogens — *Clostridium difficile*, *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 three loose stools per day [4,5], although a recent survey in spinal cord injury (SCI) centres found that definitions of diarrhoea and diagnostic criteria of *C. difficile* infection (CDI) vary between centres [6]. In addition, diarrhoea after SCI is often complicated by spurious diarrhoea due to underlying constipation.

AAD occurs in 5–25% of adult patients after 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 older and frail patients may suffer loss of dignity and 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. Risk factors reported in the literature include age [8–10], recurrent antibiotic use [8,10], hospitalization [9], severity of underlying illness [9], use of proton pump inhibitors (PPIs) [9–11] and malnutrition [12,13]. Seasonal variation [12,14,15] in CDI has been noted, although this may not be a characteristic that is shared among all patient groups [16]. Patients with SCIs are at higher risk of hospital-acquired infections because of longer hospital stay for acute and rehabilitation care [16]. Newly-injured SCI patients require anticoagulation therapy to prevent venous thromboembolism. This increases the risk of gastric ulcers, so patients often 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. difficile* compared with patients who are not taking PPIs [17]. In addition, increased use of invasive devices such as urinary catheters increases the risk of adverse effects of antibiotic use, including CDI [16,18]. In patients with SCIs, AAD and/or 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 (e.g. potassium), and chronic episodes lead to loss of micronutrients (e.g. 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: (1) to record the use of antibiotics; (2) to establish the prevalence of AAD and CDI; and (3) to assess whether there was 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 were collected from six European SCI centres on four different dates between October 2014 and June 2015. In order to analyse seasonal variations in AAD, CDI and infections caused, data from all inpatients were collected at four different time points: 1st October 2014 (autumn), 1st February 2015 (winter), 6th April 2015 (spring) and 1st June 2015 (summer). For those SCI centres with fewer than 25 beds, an additional day was allocated in each season: 15th September 2014 (autumn), 12th January 2015 (winter), 4th March 2015 (spring) and 6th July 2015 (summer).

A 30 item cross-sectional questionnaire was distributed to the clinicians at the SCI centres. 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, and presence of co-morbidities. Routine blood biochemistry and haematology data were collected +/- 3 days of study date. The second section recorded the number of medications and whether or not patients were on antibiotics. The indication for starting antibiotics; dose, route and frequency of antibiotics; and use of PPIs, H2 blockers, laxatives and antidiarrhoeal agents were also collected. The last section was aimed at determining the occurrence of diarrhoea and CDI.

Diarrhoea was defined as two or more watery stools (Bristol Stool Scale type 5, 6 or 7) over 24 h [5]. AAD was defined as two or more loose stools (Bristol Stool Scale type 5, 6 or 7) up to seven 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 medical leads at six SCI centres in four western European countries with a covering letter (addressed to the local SCI medical lead) explaining that the investigation would be used to understand the use of antibiotics in their SCI centres. The aim was to include one SCI centre for each country with 10–20 million inhabitants, and two SCI centres for countries with more than 20 million inhabitants. Participating centres were reassured that all data would be treated anonymously.