Restriction of third generation cephalosporin use reduces the incidence of *Clostridium difficile*–associated diarrhoea in hospitalised patients

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Abstract

Third generation cephalosporin antibiotics (3GC) have become the antibiotics of choice in many hospitals in recent years for the treatment of infections such as community-acquired pneumonia. However, increased use of 3GCs has also been associated with a rise in the occurrence of antibiotic-associated diarrhoea due to *Clostridium difficile*, as well as an increase in the prevalence of antibiotic resistant organisms such as methicillin resistant *Staphylococcus aureus*, vancomycin resistant entrococci, and extended-spectrum beta-lactamase–producing gram negative bacilli. In Western Australia, greater use of 3GCs was shown to correlate with more *Clostridium difficile*–associated diarrhoea (CDAD) in a large acute care teaching hospital during the 1980s. During the 1990s, the use of 3GCs in this hospital remained high and, at the end of 1998, a policy was introduced to prevent the use of ceftriaxone (the only 3GC in use) without prior approval. This resulted in a decline in 3GC use and a 50 per cent reduction in the incidence of CDAD during 1999 and 2000. To strengthen these observations, the impact of the 3GC policy on the occurrence of CDAD was analysed using time-series intervention analysis that showed a statistically significant decrease in the occurrence of CDAD during the post-intervention period after controlling for exogenous factors. Thus, changes in antibiotic prescribing practices can influence the incidence of CDAD and, potentially, antibiotic resistant pathogens. *Commun Dis Intell* 2003;27 Suppl:S28–S31.

Keywords: Clostridium difficile, Staphylococcus aureus, *antibiotic resistance*

Introduction

Clostridium difficile is an anaerobic toxin–producing bacterium, with an ability to form spores that allow it to survive in the environment for extended periods of time. Exposure to *C. difficile* can result in asymptomatic carriage or produce clinically apparent disease ranging from mild to acute diarrhoea, or the more severe pseudomembranous colitis. Mortality associated with CDAD is usually low, due to clinicians' widespread knowledge of the illness, resulting in prompt diagnosis and treatment. Information regarding the pathogenesis and clinical manifestation of CDAD is available from several reviews.[1,2,3]

The main risk factor for *C. difficile* colonisation and disease is prior exposure to antibiotics, particularly clindamycin and broad-spectrum antibiotics such as the cephalosporins.[4] Biological evidence indicates that antibiotics disrupt the normal gut flora allowing subsequent colonisation and/or infection with *C. difficile*.[3] However, not all hospitalised patients exposed to *C. difficile* become ill, or even colonised. These differences have still not been clearly explained.[5] There are different levels of risk associated with different antibiotic classes, the number of antibiotics used and the duration of antibiotic exposure, however, a paucity of good quality studies prevents firm conclusions from being drawn.[4] Increased age, patient length of hospital stay and underlying co-morbidities are important confounders

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to be considered for all hospital-acquired infections,[6] and these risk factors, in addition to the virulence of specific *C. difficile* strains,[7] may determine whether a patient develops clinical disease. The ecology and epidemiology of *C. difficile* diarrhoea are similar to that of antibiotic resistant bacteria and the incidence of CDAD may be a good surrogate measure for the impact of interventions aimed at reducing antibiotic resistance through restricting antibiotic use.

Methods and results

The Sir Charles Gairdner Hospital (SCGH) in Perth, Western Australia, is a 560-bed teaching hospital with specialist services that include neurosurgery and liver transplantation. The epidemiology of CDAD has been studied at SCGH since the early 1980s when it became apparent that this was an important hospital pathogen with the potential to cause considerable morbidity.[8] Early work showed that CDAD increased substantially during the 1980s, from 23 cases per 100,000 patient days in 1983 to 50 cases per 100,000 patient days in 1992, equating to approximately 100 cases per year.[9] At the same time third generation cephalosporin (3GC) use rose and there appeared to be a relationship between the increase in 3GC use and the incidence of CDAD.[9,10] During most of the 1990s, the incidence of CDAD remained at approximately 50 cases per 100,000 patient days annually, but unexpectedly fell to 20 cases per 100,000 patient days in 1999 and fell further still in 2000.[11] This suggested that a significant event(s) with a lasting effect took place at the end of 1998 which dramatically reduced the incidence of CDAD. No changes were made to infection control procedures at this time. While some investigators have reported significant reductions in the incidence of CDAD following changes in infection control practices,[12,13] others have found infection control strategies are relatively ineffective in reducing endemic *C. difficile* transmission.[14]

Given the previously demonstrated relationship between 3GC use and CDAD at SCGH, this relationship was re-examined. Some important changes had occurred during the period of time under investigation. A hospital-wide restriction policy on the prescription of 3GC antibiotics was introduced by the hospital Drug and Therapeutics Committee in October 1998. This involved getting approval from a clinical microbiologist or infectious diseases physician before prescribing 3GCs. Prior to this change, from 1997, ceftriaxone was the only 3GC in use at the hospital. Despite the removal of other 3GCs and the introduction of a 72-hour stop order policy at the end of 1996, the overall gram amounts of 3GCs fell no more rapidly than the decreasing trend seen since 1993. After the introduction of the restriction policy in 1998, ceftriaxone use fell from 8,000 g in 1998 to 1,400 g in 1999 and 1,200 g in 2000.[11] Although the use of 3GCs had been falling gradually during the 1990s, the introduction of the restriction policy resulted in an immediate fall to almost negligible levels. It was only when 3GC use had reached such low levels that the incidence of CDAD also fell.[11]

Time series analysis

Time series analysis is a method suitable for analysing ecologic-level data over time, which has recently been used to study the relationship between antimicrobial consumption and the evolution of resistant organisms.[15] We used time series analysis to test the effect of the change in antibiotic policy on the subsequent monthly count of CDAD episodes from 1993 to 2000.[16] Consumption of 3GC fell from 28.95 defined daily doses per 1,000 patient days (95%CI 28.63-29.26) prior to October 1998 to 3.29 defined daily doses per 1,000 patient days (95%CI 3.12-3.46) after the policy was introduced. The average incidence of CDAD during the pre-intervention period was 0.61 episodes per 1,000 patient days (95% CI 0.56-0.65). During the post-intervention period, the average incidence was 0.28 episodes per 1,000 patient days (95% CI 0.23-0.33), a statistically significant reduction. Based on our previous estimations of the cost of CDAD to SCGH,[17] such a reduction would result in a potential saving, either real or opportunity, of more than A$800,000 annually.

Discussion

Several others have reported falls in CDAD after reduced use of antibiotics known to be associated with *C. difficile* infection, such as clindamycin,[18] and cephalosporins, particularly 3GCs.[19,20,21] The aim of the policy restricting 3GC use in SCGH was not primarily to control CDAD. The policy was introduced due to concerns about increased numbers of antibiotic resistant microorganisms within the hospital. Cephalosporin use has been implicated in the increased prevalence of methicillin resistant *Staphylococcus aureus*,[22,23] vancomycin resistant enterococci,[24] and extended-spectrum beta-lactamase producing gram-negative organisms.[25] There is now increasing evidence that reduction in the use of this class of antibiotics can lead to reduced rates of methicillin resistant *Staphylococcus aureus*,[22] vancomycin resistant enterococci[25] and extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*.[25] The effectiveness of the policy introduced in SCGH is currently being evaluated regarding these types of organisms.

Although evidence from the literature indicates that a reduction in the use of antibiotics results in decreased rates of resistant organisms, the exact approaches to antibiotic control are being debated.[26,27] The requirement for approval of orders for ceftriaxone at SCGH resulted in a sustained reduction in ceftriaxone use over the 2-year period following implementation of the policy. The success of this policy must be attributed to the hospital Drug and Therapeutic Committee that regularly audits and reviews antibiotic use in the hospital. However, methods to assess the effectiveness of such interventions are contentious.[28] Using a time series approach not only accounts for auto-correlation of the data, but also controls for exogenous factors that influence the data series.[29] We have demonstrated that a restrictive prescribing policy for 3GCs can significantly reduce the incidence of CDAD and may, potentially, reduce antibiotic resistant organisms.

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