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Short report

Reduction in *Clostridium difficile* environmental contamination by hospitalized patients treated with fidaxomicin

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SUMMARY

Fidaxomicin is sporicidal and may be associated with a reduced time to resolution of diarrhoea when used to treat patients with *Clostridium difficile* infection (CDI). This study investigated whether fidaxomicin for treatment of all patients with CDI reduced *C. difficile* environmental contamination. Surfaces in the rooms of 66 hospitalized patients treated with metronidazole and/or vancomycin and 68 hospitalized patients treated with fidaxomicin were sampled. Patients treated with fidaxomicin were less likely to contaminate their environment (25/68, 36.8%) than patients treated with metronidazole and/or vancomycin (38/66 57.6%) ($P = 0.02$). Treatment with fidaxomicin was associated with reduced environmental contamination with *C. difficile*.

Introduction

Fidaxomicin has been licensed for the treatment of *Clostridium difficile* infection (CDI) since 2011. In-vitro studies have indicated that fidaxomicin exhibits bactericidal activity against *C. difficile*,[1] inhibits outgrowth of spores[2] and inhibits toxin production.[3]

Two randomized controlled trials demonstrated significantly lower recurrence rates in patients treated with fidaxomicin compared with patients treated with oral vancomycin.[4,5] In one study, the median time to resolution of diarrhoea was shorter in patients treated with fidaxomicin compared with patients treated with vancomycin (58 vs 78 h), although this was not significant.[5]

These properties could result in less bacterial shedding; however, to the authors' knowledge, no studies have investigated the effect of introducing fidaxomicin on environmental

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contamination. The authors started using fidaxomicin as a first-line therapy in all adults in October 2012. Previously, metronidazole and/or vancomycin was prescribed according to severity. Environmental contamination rates were assessed in the rooms of patients treated with metronidazole and/or vancomycin and the rooms of patients treated with fidaxomicin.

Methods

Setting

This study was conducted in an academic hospital with 1100 beds, including 180 single rooms. Patients with diarrhoea are placed in these rooms (with en-suite toilet) until at least 48 h after return to normal bowel habit, as described previously.[6] This study was classed as a service evaluation with ethical board exemption; as such, patient consent was not sought.

Investigation for CDI

Clinicians are advised to investigate all clinically significant diarrhoea using GDH enzyme immunoassay (EIA) (*C. diff* Chek-60, TechLab, Blacksburg, VA, USA), followed by EIA for toxins A/B (*C. difficile* ToxA/B II, TechLab, Blacksburg, VA, USA) and polymerase chain reaction (PCR) (GeneXpert, Cepheid, Sunnyvale, CA, USA). Patients with positive toxin EIA or positive PCR results are reviewed by an infectious diseases and/or microbiology physician who makes recommendations on treatment. If required, treatment consisted of metronidazole and/or oral vancomycin during the baseline period (April–September 2012) and fidaxomicin between October 2012 and June 2014.

Environmental cleaning

Daily cleaning is performed with a chlorine-dioxide-containing solution (Difficil-S, Clinimax Ltd, Bury St Edmunds, UK) using microfibre cloths. The rooms of all patients with *C. difficile*, meticillin-resistant *Staphylococcus aureus* or other resistant organisms are required to undergo deep/terminal cleaning upon discharge. This comprises standard cleaning as described above, followed by decontamination with a hydrogen peroxide vapour (HPV) system (Bioquell UK Ltd, Andover, UK). No changes to the environmental cleaning and disinfection policies were made during the study period.

Environmental sampling

Samples were collected between two and four days following the patient result from four standardized patient room sites: bed rails, bed controls/call buttons, toilet and shower area. Samples were collected using cellulose sponges presoaked in neutralizing buffer (Whatman, Maidstone, UK). Sponges were rubbed over a 10 cm × 10 cm area in two directions at right angles, and placed in Robertson's cooked meat broth supplemented with cycloserine, cefoxitin, lysozyme and sodium taurocholate. Samples were incubated anaerobically for seven days at 37°C as described previously.[7] Aliquots of culture broth were subcultured on to agar containing cycloserine, cefoxitin and fructose (Oxoid, Basingstoke, UK), and incubated for a further two days. Presumptive colonies were confirmed with MALDI-TOF mass spectrometry (Bruker Corp, Coventry, UK). All isolates underwent PCR ribotyping according to standard techniques.

Patient demographics (age, sex, community or hospital-associated infection), markers of severity [peripheral white cell count, C-reactive protein (CRP), albumin and creatinine; taking the most extreme value within three days of the laboratory test] and clinical outcomes (30-day all-cause mortality and length of stay) were recorded. The PCR threshold cycle (Ct) value was used as a surrogate marker of bacterial load.

Statistical methods

Continuous variables were compared using unpaired *t*-tests, and categorical variables were compared using Fisher's exact tests.

Results

In total, 66 patients who were treated with metronidazole and/or vancomycin between April and September 2012 had environmental sampling performed and were included in the study. Between October 2012 and June 2014, 68 patients treated with fidaxomicin had environmental sampling performed and were included in the study. Of the patients who were treated with metronidazole and/or vancomycin, 42 (63.7%) received metronidazole alone, 23 (34.8%) received vancomycin alone, and one (1.5%) received both metronidazole and vancomycin.

There were no significant differences in the demographics of either patient group (age and sex), whether the infection was community or hospital-associated, markers of severity (white cell count, CRP, albumin and creatinine) or 30-day all-cause mortality. There were no significant differences in the proportion of patients with a positive toxin EIA and no difference in the mean PCR Ct values (26.6 for patients treated with metronidazole and/or vancomycin vs 26 for patients treated with fidaxomicin), suggesting that the initial bioburden was similar in both groups. Patients treated with fidaxomicin had a longer length of stay following diagnosis (median 26 days) compared with patients treated with metronidazole and/or vancomycin (median 12 days) ($P = 0.01$).

Figure 1 summarizes the environmental contamination results for both patient groups. In total, 38 out of 66 (57.6%) patients treated with metronidazole and/or vancomycin had one or more positive environmental cultures compared with 25 of 68 (36.8%) patients treated with fidaxomicin ($P = 0.02$). Similarly, when considering all of the sampled environmental sites, 68 out of 264 (25.8%) were positive in patients treated with metronidazole and/or vancomycin compared with 47 out of 272 (17.3%) in patients treated with fidaxomicin ($P = 0.02$).

Patient isolates were indistinguishable from environmental isolates on PCR ribotyping in 51 out of 68 (75%) of cases for patients treated with metronidazole and/or vancomycin, and 38 out of 47 (80.1%) cases for patients treated with fidaxomicin ($P = 0.5$).

Discussion

The use of fidaxomicin as a first-line agent for all patients with CDI was associated with a decrease in environmental

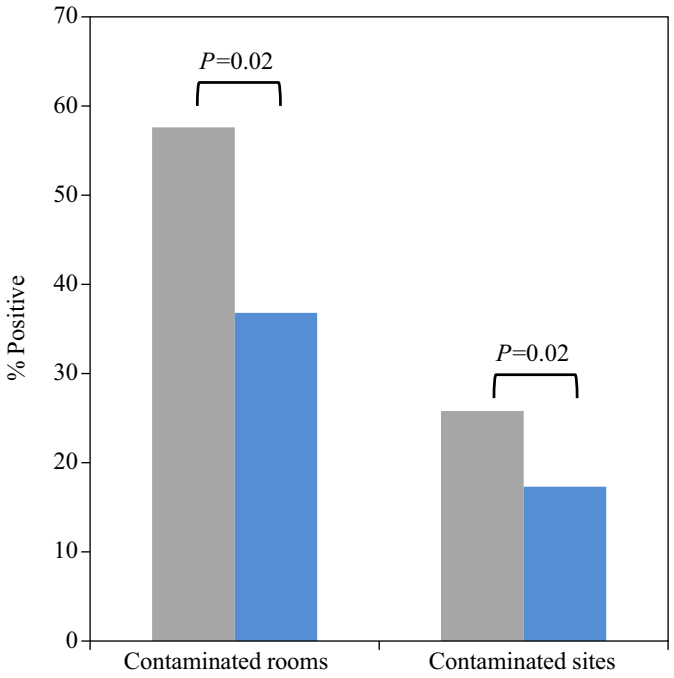

Figure 1. Environmental contamination rates for patients treated with vancomycin and/or metronidazole and fidaxomicin.

contamination, both in terms of the number of patient rooms from which *C. difficile* was recovered, and the overall burden of contamination determined by the proportion of contaminated sites. Importantly, there were no significant differences in patient groups in terms of demographics, mode of acquisition and severity markers. Additionally, likely bacterial burden using the PCR Ct value as a surrogate marker was similar in both groups; other investigators have also used this parameter to estimate bacterial load.[8] The reason for the additional length of stay for patients treated with fidaxomicin is unclear but warrants further investigation.

This study has several limitations. Firstly, time to resolution of diarrhoea was not measured, but may be an important factor in environmental contamination rates. Instead, sampling was performed between two and four days following the patient result, which may have resulted in variation in administration time of anti-*C. difficile* therapy. However, it is estimated that most patients had received at least two full days of therapy when the environmental samples were taken. Patients are likely to wait longer to receive fidaxomicin (which is a non-stock drug and provided from the central pharmacy) than metronidazole and/or vancomycin (which are stock items on all wards).

Secondly, the environmental sampling approach was qualitative, including a broth enrichment step to improve sensitivity. As such, it was not possible to evaluate differences in the concentration of contamination on surfaces.

The rate of CDI declined during the study [from 18.25 cases per 100,000 occupied bed days (OBD) from April to September 2012 to 13.21 cases per 100,000 OBD from October 2012 to June 2014]. Although there were no changes in environmental cleaning during this period, there were some additional infection control interventions (particularly around antimicrobial stewardship) that were introduced during the course of the study. It is possible that the reduction in environmental contamination was partly due to these additional interventions rather than use of fidaxomicin.

Not all of the environmental isolates matched the clinical isolates; overall, 75% and 80.1% of isolates matched in patients treated with metronidazole and/or vancomycin and fidaxomicin, respectively. More discriminatory genotyping methods, such as multi-locus variable number tandem repeat analysis or whole-genome sequencing, were not performed, and may have revealed fewer matching isolates. The source of these non-matching isolates is unclear. However, the most likely source is from prior occupants who were not recognized to be infected or colonized with *C. difficile*, and whose rooms were not therefore decontaminated with HPV.

A prior room occupant with CDI is a significant risk factor for CDI acquisition.[9] As HPV was used to decontaminate the rooms of CDI patients, any increased risk for the incoming occupant associated with higher levels of contamination in the rooms of patients treated using metronidazole and/or vancomycin should be mitigated. However, the higher levels of contamination during the patient's stay are important from an infection prevention viewpoint, and likely increase the risk of hand contamination of healthcare workers during patient care.[10]

Treatment with fidaxomicin was associated with significantly decreased environmental contamination compared with treatment with metronidazole and/or vancomycin. To the authors' knowledge, this is the first study to describe such an association. Fidaxomicin may contribute to reduction of secondary cases of CDI by reducing contamination of the environment, although the exact mechanism for this is not known.

Conflict of interest statement

SG discloses consultancy, speakers' fees, educational grants and research relationships with Astellas Pharma. PW discloses consultancy, speakers' fees and educational grants from Astellas Pharma. JAO is employed part-time by Bioquell.

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