A novel strategy for designing optimal antibiotic stewardships using *Clostridium difficile* as an exemplar

M.A. Aldeyab[1], S. Harbarth[2], N. Vernaz[2], M.P. Kearney[3], M.G. Scott[3], C. Funston[3], K. Savage[3], D. Kelly[3], F.A. Magee[3], G. Conlon[3], M.A. Aldiab[4], J.C. McElnay[1]
[1]Academic Practice Unit, Northern Health and Social Care Trust/Queen's University Belfast,
[2]University of Geneva Hospitals and Medical School, Geneva, Switzerland,
[3]Antrim Area Hospital, Northern Trust, 45 Bush Road, Antrim BT42 2RL,
[4]German-Jordanian University, School of Informatics and Computing, Amman, Jordan.

INTRODUCTION

Inappropriate antimicrobial use has been associated with increased morbidity, mortality and hospital costs. As antimicrobial use is considered a major determinant in the evolution of resistance,[1] hospital antibiotic stewardships programmes has been developed for the prevention and containment of antimicrobial resistance.[2] Determining classes of antibiotics to be restricted/cycled and optimal time intervals required for an antibiotic restriction/cycling policy is considered a key aspect, and should be informed by local epidemiology data. The objective of the presented work was to evaluate temporal relationships existing between antimicrobial drug use and the incidence of *Clostridium difficile* Infection (CDI) in Antrim Area Hospital, thus providing theoretical basis for designing efficient antibiotic stewardships. This was achieved using time-series analysis technique which considered the strongest quasi-experimental method to ascertain the longitudinal effects of healthcare interventions.[3]

METHODS

- Data: The present retrospective investigation involved collecting data on a monthly basis on the usage of antibiotics and, gastric-acid suppressive agents, and on infection control practices together with the incidence of CDI within Antrim Area Hospital over a five-year period (February 2002- March 2007). The study was ecological in design.
- Pharmacy and microbiology data: The monthly quantities of each antimicrobial agent delivered to each ward of the hospital were obtained from the pharmacy information system and were converted into defined daily doses (DDDs). Similarly, monthly quantities of gastric-acid suppressive agents i.e. proton pump inhibitors (PPIs)and histamine-2 receptor antagonists (H2RAs) were determined. CDI cases per month were obtained from the clinical microbiology information system over the study period. All variables were adjusted per 100 bed-days.
- Infection control practices: Details on infection control practices i.e. data on usage of chlorhexidine (liters) and alcohol-based hand rub (liters), and data on staffing levels of nurses/auxiliary nurses were obtained at monthly intervals. All variables were adjusted per 100 bed-days.
- Statistical methods: A multivariate autoregressive integrated moving average (ARIMA) model was built to relate CDI incidence with antibiotic use, the use of gastric-acid suppressive agents and the level of infection control practices. Data were analysed using Eviews 6.0 (Quantitative Micro Software, Irvine, California, USA).

RESULTS

Time series analysis showed that CDI incidence had a positive relationship with the use of second-generation cephalosporins, third-generation cephalosporins, fluoroquinolones, amoxicillin-clavulanic acid, macrolides and H2RAs with various time lags (Table 1).

Table 1. Multivariate time-series analysis model for monthly CDI incidence (R^2 = 0.78).

Term	Lag time [a]	Coefficient [b]	P-value
Second-generation cephalosporin use	2	0.010299	0.0038
Third-generation cephalosporin use	2	0.018226	0.0059
Fluoroquinolone use	3	0.003835	0.0016
Amoxicillin-clavulanic acid use	1	0.001518	0.0024
Macrolide use	5	0.001835	0.0317
H2-receptor antagonist use	1	0.001035	0.0035

[a] Represents the delay necessary to observe the effect (in months).

[b] Indicates the size and the direction of the effect.

For example, temporal variations in CDI incidence followed temporal variations in second-generation cephalosporin use with an average delay of two months. This means that, on average, an increase (or decrease) of second-generation cephalosporin use by 1 DDD/100 bed-days resulted two months later in an increase (or decrease) of the incidence of CDI by 0.01/100 bed-days. Projections for Antrim Area Hospital on the DDDs of the implicated agents and the numbers of patients needed to be treated to cause or prevent one CDI case at the hospital are presented in Table 2.

Table 2. Projections for the Antrim Area Hospital on the required usage of DDDs and on the number of patients needed to be treated to cause or prevent the occurrence of one CDI case.

Term	Lag time [a]	DDDs [b]	No. Patients [c]
Second-generation cephalosporin	2	97	14
Third-generation cephalosporin	2	55	8
Fluoroquinolone	3	261	37
Amoxicillin-clavulanic acid	1	659	94
Macrolide	5	545	78
Histamine-2 receptor antagonists	1	966	na [d]

[a] Represents the delay necessary to observe the effect (in months).

[b] Represents the number of Defined Daily Doses (DDD) needed on a given month to contribute to the occurrence of one CDI case.

[c] For antimicrobials, this represents number of patients needed to be treated on a given month to cause the occurrence of one CDI case. This number was based on the assumption of an average treatment course of 7 DDD.

[d] na , not applicable.

No correlation was found between PPI use, nursing levels and infection control practices and the incidence of CDI. The determination coefficient (R^2) of the final model was 0.78, i.e. 78 % of the variation in the incidence of CDI over the study period was explained by the factors included in the model.

DISCUSSION

- The findings of this study confirm that the restriction of specific antibiotics could reduce the incidence of CDI, but further prospective work is required to investigate the feasibility of restricting those antibiotics and into appropriate alternatives during restriction periods.
- The results of this research can help hospitals to set priorities for restricting the use of specific antibiotic classes, based on the size-effect of each class and the delay necessary to observe an effect.
- Measuring the delay required to observe an effect following the restriction/use of particular antibiotics, which was possible using the time-series analysis technique, could be a possible way forward in determining the optimal time required for an antibiotic restriction policy.

REFERENCES

1- Gyssens IC. Quality measures of antimicrobial drug use. Int J Antimicrob Agents 2001; 17:9-19.
2- MacDougall C, Polk RE. Antimicrobial stewardship programs in health care systems. Clin Microbiol Rev 2005; 18:638-56.
3- Aldeyab MA, Harbarth S, Vernaz N, Kearney MP, Scott MG, Funston C, Savage K, Kelly D, Aldiab M, McElnay JC. Quasiexperimental study of the effects of antibiotic use, gastric acid-suppressive agents, and infection control practices on the incidence of Clostridium difficile-associated diarrhea in hospitalized patients.. Antimicrobial Agents and Chemotherapy 2009; 53:2082-8.