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Starting a movement: An epidemiological audit into the distribution and determinants of *Clostridium Difficele* infection at an Australian tertiary hospital site

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BRIEF REPORT

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ABSTRACT

Background
The emergence of hypervirulent strains of *Clostridioides (Clostridium) difficile* over the past few decades has cemented *C. difficile* infection (CDI) as the most common cause of nosocomial infectious diarrhoea within Australia. This report was initiated to better understand the burden of disease at the Bankstown-Lidcombe Hospital through analysis of CDI incidence, risk factors, and treatment.

Aims
The specific objectives of this study were two-fold; 1) to determine the prevalence of hospitalised patients affected with CDI and 2) to identify risk factors for CDI in hospitalised patients.

Methods
A retrospective review of all consecutive CDI cases at the Bankstown-Lidcombe Hospital between 1 July 2014 and 31 December 2018 was performed. CDI incidence was calculated based on the number of CDI cases observed per 10,000 patient days. Annual incidence and predisposing antibiotics to CDI were compared via univariate analysis and Student t-tests. Treatment for CDI was compared using contingency analysis via Pearson's chi-squared analysis.

Results
The CDI diagnoses ranged from 3.2–4.6 (as a proportion of 10,000 occupied bed days) throughout 2014 and 2018. There was a significant decrease in CDI associated with Macrolides between 2017 and 2018 (p=0.03). There was a significant rise in CDI associated with Beta lactamase inhibitors and Penicillins (e.g., Tazobactam/Piperacillin). The majority of CDI patients were treated with single therapy metronidazole during their hospital stays.

Conclusion
CDI risk minimisation presents a significant challenge to all hospital departments. This audit highlights the importance of antibiotic usage influencing in-patient CDI cases and the vital role of multidisciplinary teams (microbiologists, pathologists, physicians, surgeons and pharmacists) in managing and monitoring these patients.

Key Words
Clostridioides difficele, Clostridium difficele, epidemiology, risk factors

Implications for Practice:

1. What is known about this subject?
The epidemiology of CDI is dynamically evolving with the emergence of hypervirulent strains and a global rise in disease incidence over the past two decades.

2. What new information is offered in this report?
This report highlights the importance of antibiotic usage influencing in-patient CDI cases and the vital role of multidisciplinary teams in managing and monitoring these patients.

3. What are the implications for research, policy, or practice?
Monitoring prescribing patterns and educating about antibiotic usage will maximise patient safety and minimise financial cost relating to CDI.

Background

Clostridioides (Clostridium) difficile infection (CDI) is the most common cause of nosocomial infectious diarrhoea and an ongoing significant challenge for healthcare services.[1-3] Multiple studies have documented its clinical and economic consequences; patients with CDI have longer inpatient stays, are more frequently readmitted to hospital, are less likely to be discharged directly home and require more investigations/therapies.[4-6] Information on the costs of CDI varies, with primary infection costs ranging from USD $3,400–$16,300 per case.[7] Additionally, the epidemiology of CDI is dynamically evolving with the emergence of hypervirulent strains and a global rise in disease incidence over the past two decades.[8]

However, surveillance of CDI within Australia remains poor. While most states use laboratory-based surveillance to monitor cases of hospital identified CDI, there is variable surveillance of exposure risk, disease severity and recurrence.[9]

This audit was initiated to better understand the burden of disease at the Bankstown-Lidcombe Hospital through analysis of CDI incidence, risk factors, and treatment. The specific objectives of this study were two-fold; 1) to determine the prevalence of hospitalised patients inflicted with CDI and 2) to identify risk factors for CDI in hospitalised patients.

Case details/Method

A retrospective review of all consecutive CDI cases at the Bankstown-Lidcombe Hospital – a 450 bed tertiary care teaching hospital in Sydney, NSW – between 1 July 2014 and 31 December 2018 was performed. Patients aged 18 years or older were included in the study. Further inclusion criteria included antibiotic therapy being provided for the first time during the study/audit period. The duration of antibiotic therapy was variable but ranged from three days to several weeks.

This was an audit study and was part of the surgical, infectious disease and pharmacy department's clinical governance programme. It used anonymized confidential routinely collected data. The policy of our institution is that ethical approval is not required for audit projects. There was no funding for this study. The author(s) declared no potential conflicts of interest with respect to the research and authorship.

The Public Health Laboratory Network laboratory case definition was used to diagnose CDI
This involved:
a) laboratory detection of C. difficile toxins and/or toxigenic *C. difficile* in faeces, rectal swab or bowel contents AND
b) relevant clinical manifestations, e.g., diarrhoea or, ileus, toxic megacolon or pseudomembranous colitis.[10]

Diarrhoea was defined as three or more loose bowel motions within 24 hours. Inpatients with diarrhoea, whose stool samples were positive for *C. difficile* toxin Real-Time Polymerase Chain Reaction (RT-PCR) tests 48 hours after admission or within four weeks of discharge were diagnosed as CDI positive. CDI toxin assay findings may remain positive for several months.[11] As such, positive repeat toxin assay results requested within eight weeks of a previously positive *C. difficile* toxin assay result were excluded from the study.

CDI resolution was defined as a cessation of diarrhoea for at least 3 days or upon discharge from hospital.[12]

The demographic and clinical characteristics of the patients are documented (Table 1). Unless otherwise stated, all results are expressed as the mean±standard error.

Microbiological data

Stool samples were collected by the patient's bedside nurse and transported to the clinical microbiology laboratory as per usual clinical protocol. Stool was analysed for the presence of genes encoding *C. difficile* toxin B or the toxin regulatory gene through RT-PCR directly from the stool sample.

Hospital practices

In 2012 the Australian Commission on Safety and Quality in Health Care introduced the antimicrobial stewardship (AMS) criterion in the new National Safety and Quality in Health Service Standards (NSQHS).[13] In August 2014, Bankstown-Lidcombe Hospital had established a Guidance AMS programme. Infectious disease consultants who were already well known in the institution were selected to participate in the AMS program on a consultative basis. Together with a medical microbiologist, pharmacist, nursing representatives from infection prevention and executive representatives, they formed the AMS committee (AMSC). The AMSC was responsible for ensuring compliance with the

NSQHS standards. A small subgroup – the AMS team (AMST) – was responsible for implementing and directing the activities of the AMS programme on the wards. The AMST comprised of ID physicians, pharmacist and infection control nurses.

Elements of the AMS programme include formulary restriction (requiring web-based approval for most broad-spectrum antimicrobials or specific approval from an infectious disease physician for selected agents), education of prescribers and drug use evaluations and reporting to unit heads on trends of antimicrobial use.

There were no changes in isolation requirements, education programmes, personal protection equipment protocols and disinfection routines between 2014 and 2019.

Data collection and statistical analysis

All CDI patient data were collected through the secured electronic hospital database, including patient age, gender, date of admission, prior underlying diseases, prior medication and prior surgery. Where required, further history on previous hospitalisation, antibiotic use, and symptoms was obtained through participant interview.

Annual CDI incidence was calculated based on the number of nosocomial CDI cases per 10,000 patient days. Antibiotic consumption is expressed as Defined Daily Doses (DDD) – the assumed average maintenance dose per day for a drug used for its main indication in adults.[14] This was to facilitate objective comparisons between prescribing patterns and effectively document the relative therapeutic intensity amongst drug groups.

Monthly CDI incidence was calculated as a ratio of DDD using the following equation:

$$\frac{\text{Monthly CDI}}{\text{DDD}} \times 10{,}000$$

Antibiotics were classified into the following subgroups as per Table 2.

Continuous data were compared in the univariate analysis Student t-test or one-way/multivariate analysis of variance. Nominal variables were expressed as number/percentage and compared using contingency analysis including calculating the Likelihood Ratio, and undertaking Pearson's chi-squared analysis.

Statistical analysis was performed using JMP statistical software package for Macintosh version 10 (SAS, Cary, NC). A value of $p<0.05$ was considered significant.

Data quality and reliability for this study were ensured through a joint effort between the clinical records department, Infectious Disease Control Unit, Antimicrobial Stewardship Committee and the General Surgery team. Data were de-identified at the time of analysis and submission. At all times the confidentiality of individual patients' and the hospitals' data was maintained. All electronic media containing patient specific data meet the requirements of health service data protection and encryption standards.

Results

A total of 285 consecutive patients were admitted to hospital with CDI between the specified dates. Of these, four were excluded due to being under 18 years of age. This resulted in 281 patients who were enrolled in the study and constituted the final study sample.

Overall, the trend in CDI diagnoses as a proportion of 10,000 occupied bed days remained stable between 2014 and 2018. This was despite a substantial increase from 3.2–4.6 CDI diagnoses per 10,000 patient days, which lead to a trend towards significance from 2014 and 2015 (p=0.081). This is demonstrated in Figure 1.

Despite the above trend to significance, One-way Analysis of Variance analysing the monthly CDI cases as a proportion of 10,000 DDD revealed that the inciting antibiotics involved in CDI did not have significant increases. Interestingly, using the Student-t analysis, there was a significant rise in CDI associated with Beta lactamase inhibitors upon comparing the two periods "2014 and 2018" (p=0.03) and "2016 and 2018" (p=0.01). Following this, there was a trend to significance for a rise in CDI associated with penicillins between 2016 and 2018 (p=0.06).

Conversely, there was a significant decrease in CDI associated with Macrolides between 2017 and 2018 (p=0.03).

The association between CDI cases and DDD is represented graphically in Figure 3.

All patients were treated with antibiotics for what were considered clinically significant infections. There was 80.0-90.3 per cent compliance rate with guidelines regarding antibiotic choice (metronidazole and/or vancomycin)

between 2014 and 2018. There were nil significant changes to the prescribing compliance rate, as shown in Figure 4 below. Patient ward and/or admitting specialty was not associated with a particular inciting antibiotic or length of stay.

The majority of CDI patients were treated with single therapy metronidazole during their hospital stays. Treatment with metronidazole was consistent across all wards. In contrast, vancomycin use significantly varied between wards. Length of stay was not affected by treatment. The Chi-squared graphical representations are included in Figure 5 for metronidazole and/or vancomycin. Furthermore, other prescribed antibiotics during the 2014 to 2018 period included rifaxamine, cephalexin, ceftriaxone, gentamycin, and ciprofloxacin. Graphs are not provided for these latter antibiotics as 20 per cent of their Chi-squared analysis cells have an expected count of less than five, making the statistical analysis underpowered.

Discussion

Inciting antibiotics

Antimicrobial drug use is the single most important risk factor for CDI.[15] Larger doses, duration and number of prescriptions all result in a greater degree of normal gut flora depletion. Of these, macrolides (particularly clarithromycin) have been proposed to be a risk factor for the development of CDI and *C. difficile* toxin positive nosocomial diarrhoea.[16] Reassuringly, macrolide usage at our institution revealed a reduced association with CDI between 2017 and 2018. This trend for macrolides bears particular importance as it theoretically holds a moderately elevated CDI risk with an Odds Ratio ranging from 2.20–4.01. For comparison, penicillins have an Odds Ratio of approximately 2.71.[17]

Lincosamide (i.e., Clindamycin) associated CDI at our institution has also been minimal. As a high risk antibiotic, clindamycin is known to impair intestinal microbiota diversity from its first dose, predisposing to and being extensively associated with CDI.[18] For comparison, clindamycin holds an Odds Ratio ranging from 2.12– 42.[18]

Such trends over time emphasise the strong clinical practice and judgement of antibiotic usage/review by the medical and pharmaceutical teams. The implementation of Guidance AMS Programme at our institution from 2014 onwards has had a profound impact on optimising safe antibiotic use with the most notable changes occurring in 2015 and 2016. This reflects the known background that AMS programmes complement environmental and infection control interventions in controlling antibiotic use, and improves the incidence of CDI.[19]

Unfortunately, these trends have not extended to all antibiotic types. Tazobactam/Piperacillin, which has a profoundly deleterious effect on gut flora and an elevated CDI risk profile,[20] has been increasingly associated with inpatient CDI cases within the 2014–2018 period at out institution. While the exact pathogenesis between tazobactam/piperacillin usage and CDI remains unknown, it is suspected that post tazobactam/piperacillin administration, there is a complex interplay between the *C. difficile* toxins and gut biofilm constituents.

Prevalence

Overall, the trend in CDI diagnoses as a proportion of 10,000 occupied bed days remained stable between 2014 and 2018. This was despite a substantial increase from 3.2–4.6 CDI diagnoses per 10,000 patient days, which lead to a trend towards significance from 2014 and 2015 (p=0.081). This is demonstrated in Figure 1.

The trend in CDI cases remained stable between 2014 and 2018 at Bankstown-Lidcombe Hospital, ranging from 3.2–4.6 cases per 10,000 occupied bed days. These incidence rates are similar to those found Australia wide, with CDI incidence at 3.2, 4.4 and 4.3 per 10,000 patient days in 2011, 2013 and 2016, respectively.[21]

The peaks in CDI cases during this period are likely to be related to hypervirulent strains of *C. difficile*. Recently, a hypervirulent strain (PCR ribotype 027) has been associated with high rates of nosocomial transmission, severe disease and increased mortality, particularly in patients aged over 65 years.[22] Overall, extrapolation and interpretation of the CDI prevalence within Bankstown, NSW and Australia is difficult to undertake due to the lack of consistent data and the high amount of variability in epidemiology results between the territories and states.

Treatment

There are currently several published guidelines for the treatment of CDI and most recommend the use of metronidazole for mild-to-moderate cases of CDI and vancomycin in most severe conditions.[23] The suggested scoring criteria for CDI severity and summary of the recommended treatments are outlined below in Table 3.[24]

Within the CDI cohort, the majority of patients (80–90.32 per cent) were prescribed metronidazole and/or vancomycin appropriately. This audit has categorised both

metronidazole and/or vancomycin as appropriate initial therapy for CDI. This follows the conclusions of recent observational studies which suggest that the effectiveness of vancomycin and metronidazole are similar since the emergence of the hypervirulent *C. difficile* PCR ribotype 027.[25]

Tigecycline and fusidic acid have been studied and considered as alternative therapies for mild to moderate disease in patients for whom metronidazole is contraindicated. However, there are only small case series supporting the use of tigecycline,[26] and fusidic acid may be less efficacious than vancomycin.[27] None of the cohort patients within our audit were initiated on these antibiotics secondary to the restricted antibiotic policy. This policy was selected by our pharmacy department to simplify education of junior medical staff and increase hospital-wide familiarity with the drugs used.

There were several limitations to this retrospective epidemiological study, as the required information was limited to the data available in the electronic and paper medical records at the time of data collection. Another limitation was that our audit was not designed to assess the reason for initial antibiotic choice, antibiotic escalation, and duration of antibiotic therapy.

Conclusion

CDI risk minimisation presents a significant challenge to all hospital departments. This audit highlights the importance of antibiotic usage influencing in-patient CDI cases and the vital role of multidisciplinary teams (microbiologists, pathologists, physicians, surgeons and pharmacists) in managing and monitoring these patients. As such, it is recommended that prescribing patterns should be monitored and discussed with pharmacy, leadership, and physicians. Such efforts take time but in the long run, documentation, monitoring, education, and close follow-up of the most appropriate use of antibiotics will maximise patient safety and minimise financial cost in a sustainable manner.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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None

ETHICS COMMITTEE APPROVAL

The ethics approval committee at our local hospital district deemed approval was not required for this audit.

Table 1: Patient demographic and clinical characteristics[†]

Main demographics	n=281
Gender	
Male	123 (43.8)
Female	158 (56.2)
Mean Age±SD (years)	72.3±17.9
Recent antibiotic use	214 (74.56%)
Length of stay (Mean±SD)	24.5±27.0
Recent antibiotics	263

[†]Unless otherwise stated, values are the number (percentage) of patients. SD = standard deviation;

Table 2: Antibiotic subgroups

Antibiotic group	Antibiotics	CDI cases (n)	DDD (n)
Penicillins	Benzylpenicillin, Amoxycillin, Ampicillin, Flucloxacillin, Piperacillin	97	368,594
Cephalosporins	Cefalexin, Cefazolin, Cefepime, Ceftriaxone	79	314,165
Trimethoprim	-	6	19,181
Aminoglycosides	Gentamycin	13	48,576
Macrolides	Azithromycin, Roxithromycin	6	44,237
Lincosamides	Clindamycin	9	33,524
Tetracyclines	Doxycycline	5	37,010
Fluoroquinolones	Ciprofloxacin, Moxifloxacin, Norfloxacin	15	30,087
Beta lactamase Inhibitors	Tazobactam	67	70,279
Carbapenems	Meropenem, Ertapenem	5	8,804

Figure 1: Rate of CDI diagnoses in Bankstown-Lidcombe Hospital, 2014-2018

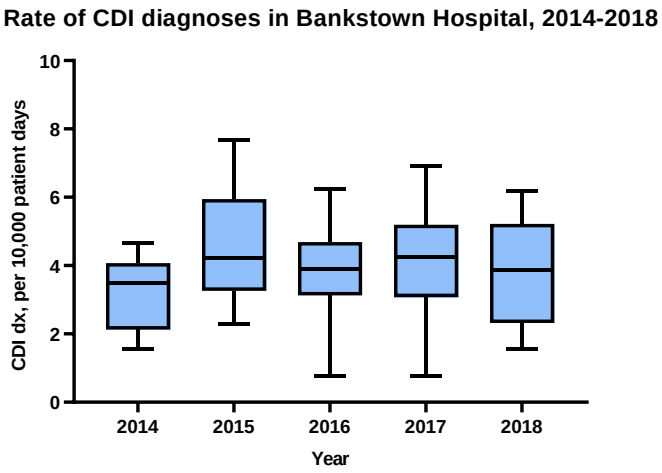


Figure 2: Bankstown-Lidcombe Hospital CDI admissions by specialty

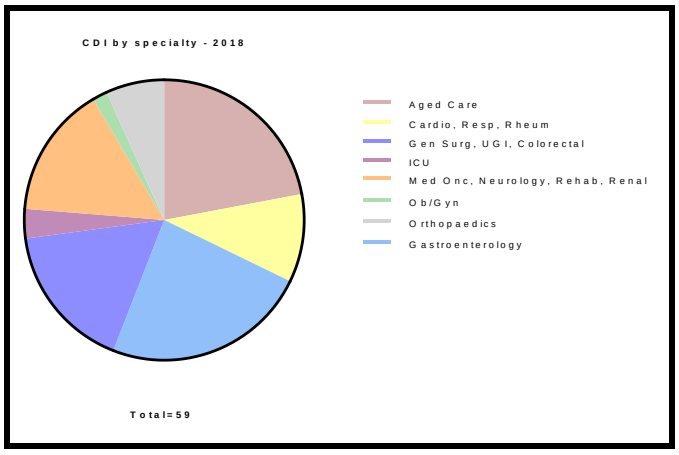
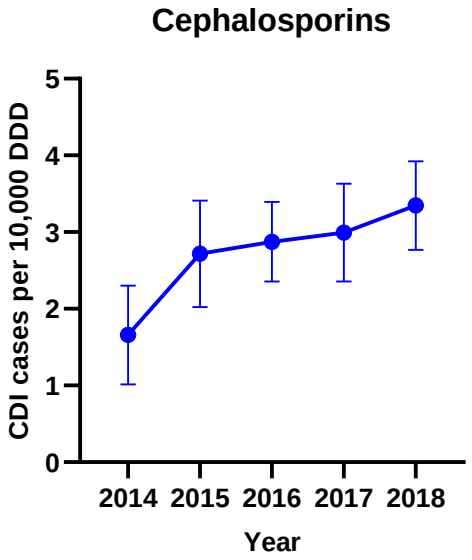
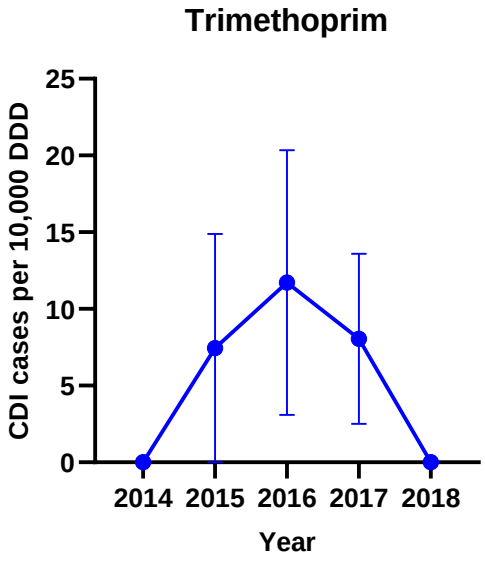
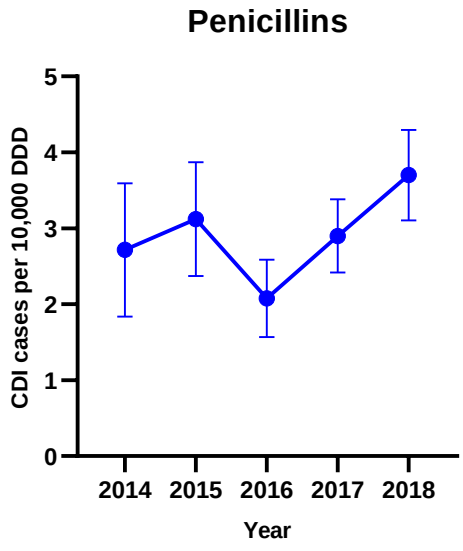
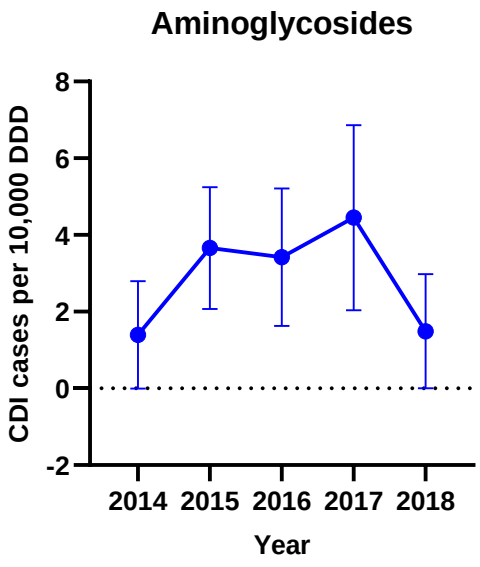


Figure 3: Association between CDI and antibiotics









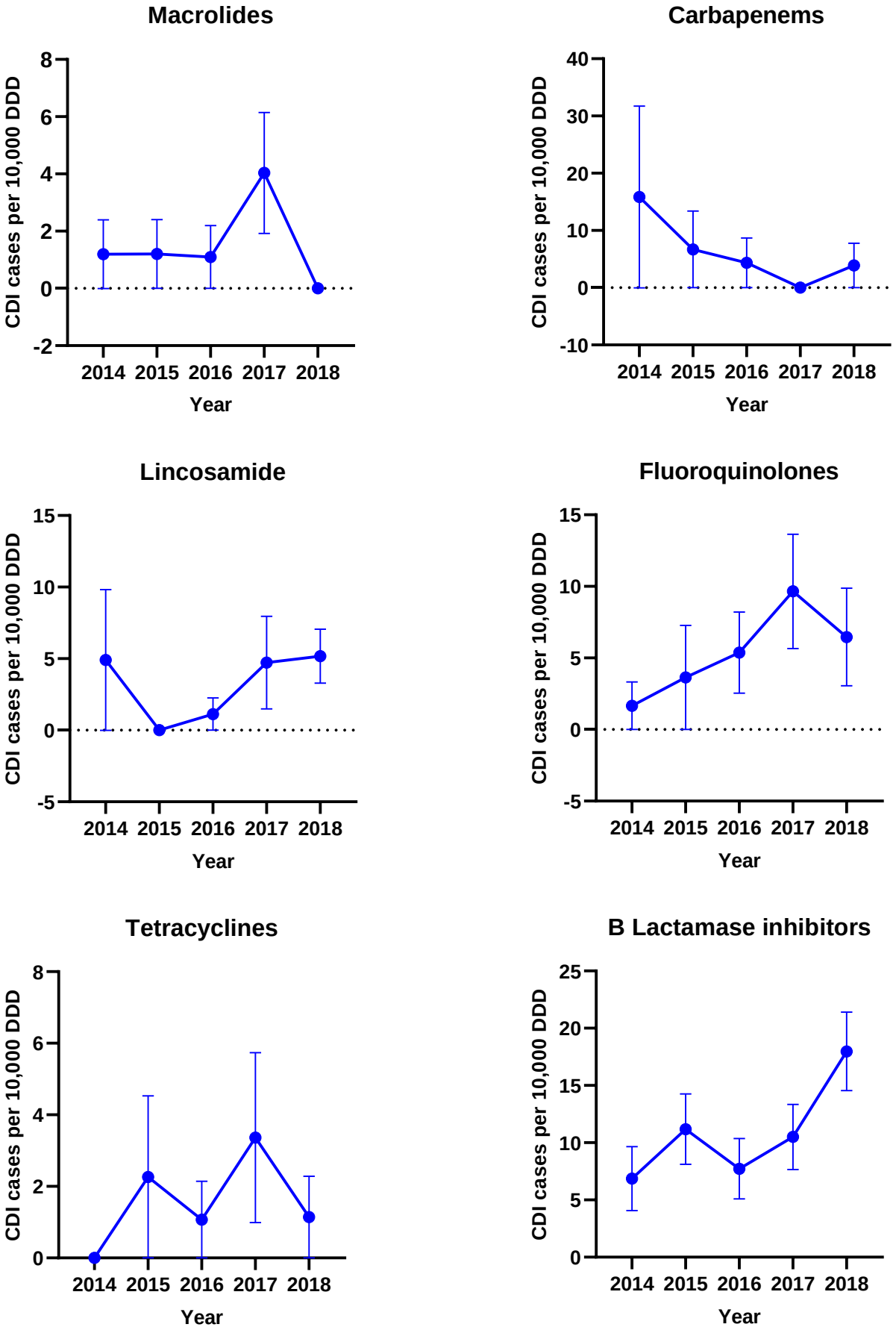

Macrolides
CDI cases per 10,000 DDD
8
6
4
2
0
-2
2014 2015 2016 2017 2018
Year
Carbapenems
CDI cases per 10,000 DDD
40
30
20
10
0
-10
2014 2015 2016 2017 2018
Year
Lincosamide
CDI cases per 10,000 DDD
15
10
5
0
-5
2014 2015 2016 2017 2018
Year
Fluoroquinolones
CDI cases per 10,000 DDD
15
10
5
0
-5
2014 2015 2016 2017 2018
Year
Tetracyclines
CDI cases per 10,000 DDD
8
6
4
2
0
2014 2015 2016 2017 2018
Year
B Lactamase inhibitors
CDI cases per 10,000 DDD
25
20
15
10
5
0
2014 2015 2016 2017 2018
Year

Figure 4: CDI and compliance with treatment guidelines

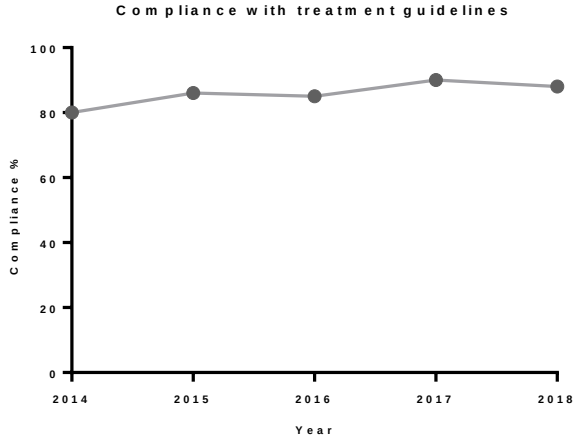


Figure 5: CDI and prescribed antibiotics by year

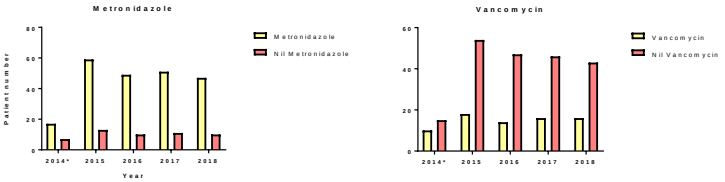


Table 3: Recommended treatment for CDI

Severity	Criteria	Treatment
Mild to moderate	Diarrhoea	Metronidazole 500mg TDS PO for 10 days If unable to take metronidazole, Vancomycin 125mg QID PO for 10 days
Severe	Serum albumin <3g/dL plus ONE of the following - WCC >15000 cells/mm3 - Abdominal tenderness	Vancomycin 125mg QID PO for 10 days
Severe and complicated	Any of the following attributable to CDI - Admission to ICU - Hypotension - Fever >38.5C - Ileus - Mental state changes - WCC >35,000 cells/mm3 - Serum lactate >2.2 - End organ failure	Vancomycin 500mg QID PO for 10 days AND Metronidazole 500mg Q8H IV AND Vancomycin 500mg (in 500ml normal saline 0.9%) QID