Successful use of feedback to improve antibiotic prescribing and reduce Clostridium difficile infection: a controlled interrupted time series

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Objectives: To investigate the effect of reinforcing a narrow-spectrum antibiotic policy on antibiotic prescription and Clostridium difficile infection (CDI) rates by feedback of antibiotic use to doctors, as part of a departmental audit and feedback programme.

Design: A prospective controlled interrupted time-series (ITS) study, with pre-defined pre- and post-intervention periods, each of 21 months.

Setting: Three acute medical wards for elderly people in a teaching hospital.

Participants: Six thousand one hundred and twenty-nine consecutive unselected acute medical admissions aged ≥80 years.

Interventions: A ‘narrow-spectrum’ antibiotic policy (reinforced by an established programme of audit and feedback of antibiotic usage and CDI rates) was introduced, following an unplanned rise in amoxicillin/clavulanic acid (Augmentin) use. It targeted broad-spectrum antibiotics for reduction (cephalosporins and amoxicillin/clavulanic acid) and narrow-spectrum antibiotics for increase (benzyl penicillin, amoxicillin and trimethoprim). Changes in the use of targeted antibiotics (intervention group) were compared with those of untargeted antibiotics (control group) using segmented regression analysis. Changes in CDI rates were examined by the Poisson regression model. Methicillin-resistant Staphylococcus aureus (MRSA) acquisition rates acted as an additional control.

Results: There was a reduction in the use of all targeted broad-spectrum antibiotics and an increase in all targeted narrow-spectrum antibiotics, statistically significant for sudden change and/or linear trend. All other antibiotic use remained unchanged. CDI rates fell with incidence rate ratios of 0.35 (0.17, 0.73) (P = 0.009). MRSA incidence did not change [0.79 (0.49, 1.28); P = 0.32].

Conclusions: This is the first controlled prospective ITS study to use feedback to reinforce antibiotic policy and reduce CDI. Multicentre ITS or cluster randomized trials of this and other methods need to be undertaken to establish the most effective means of optimizing antibiotic use and reducing CDI.

Keywords: C. difficile, safety, antibiotic-associated diarrhoea, antibiotic policy, infection control, quality assurance, prescription rates, nosocomial infections, cephalosporins, antibiotic prescription

Introduction

Clostridium difficile infection (CDI) is an increasingly common healthcare-associated infection, affecting primarily elderly patients, and is subject to mandatory surveillance in the UK.¹⁻³ It is a consequence of rising broad-spectrum antibiotic use, such as third-generation cephalosporins and amoxicillin/clavulanate.¹

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References

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policies1–3 and suggest a variety of methods to ensure these are implemented, commenting that ‘despite the apparent increased awareness of CDI and its link with antibiotic use, levels of infection are still rising and prescribing behaviour needs to be addressed’.1 The Health Care Commission surveyed all NHS Trusts in 2005 and reported that 38% did not restrict broad-spectrum antibiotic use.4 Systematic review of interventions to improve prescribing,5 including those that examine the effect on CDI, showed that nearly all were poor-quality unplanned studies with no control groups or outcomes and inadequate statistical analysis. Well-designed interrupted time-series (ITS) studies with control outcomes would provide much stronger evidence of the effectiveness of interventions, facilitate synthesis of evidence from different studies and help prioritize interventions for definitive multicentre randomized controlled trials (RCTs).7,8 Systematic reviews9,10 suggest feedback may change healthcare workers’ implementation of evidence-based guidelines, although feedback is not mentioned in national guidelines as a way of ‘addressing prescribing behaviour’.1 We have previously described the use of feedback in this context11 and now report a subsequent prospective controlled interrupted time-series study, arising from our department’s clinical audit programme, which investigated the effect of reinforcing a narrow-spectrum antibiotic policy by feeding back the use of antibiotics and CDI rates to doctors working on acute-care medical wards for the elderly where CDI was endemic.

Materials and methods

Setting
Three acute-care wards for the elderly (78 beds), admitting consecutive, unselected general medical emergency admissions over the age of 80 years, where a cephalosporin restrictive antibiotic policy with audit and feedback of antibiotic use and CDI rates was in place to reduce levels of CDI.11

<table>
<thead>
<tr>
<th>Setting: three acute-care wards for the elderly (78 beds) in 1200 bed tertiary hospital with 0.3 WTE ICD and 4.5 WTE ICNs</th>
<th>Dates: 1 September 1999 to 31 March 2003</th>
<th>Population characteristics: 6129 unselected acute consecutive unselected elderly medical emergency admissions (80 years plus). Monthly length of stay 11.93–13.53 days. Endemic CDI and E-MRSA 15 and 16. No inter-hospital transfers.</th>
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<tr>
<th>Major infection control changes during the study:</th>
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<tbody>
<tr>
<td>Cephalosporin restrictive antibiotic policy details (phase 1): community-acquired pneumonia (CAP), amoxicillin; urinary tract infection (UTI), trimethoprim; cellulitis, fluoroquinolone and benzyl penicillin; community-acquired aspiration pneumonia, benzyl penicillin and metronidazole.</td>
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</tr>
<tr>
<td>Ceftriaxone reserved for: (i) severe CAP; (ii) hospital-acquired aspiration pneumonia and (iii) UTI with renal failure.</td>
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<tr>
<td>Gentamicin: UTI with shock, septicemia with no apparent focus infection and intra-abdominal sepsis (with ampicillin and metronidazole); erythromycin: penicillin allergy</td>
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<tr>
<td>Isolation details (both phases): Ten side rooms available in the three wards. One four-bedded MRSA cohort in one ward. All other beds configured in four-bedded bays. Wall-mounted liquid soap and alcohol handrub dispenser and sink in each side room. One sink for each four-bedded bay with liquid soap and, from January 2002, one wall-mounted alcohol handrub dispenser per four-bedded bay.</td>
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<tr>
<td>MRSA screening policy (both phases): admission screening (nose, perineum, wounds and devices) of admissions from nursing homes and of those with a past history of MRSA (both groups admitted to side room). Patients screened during admission if they had been in the same bay with a new case of MRSA.</td>
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<tr>
<td>MRSA eradication policy (both phases): intranasal mupirocin and chlorhexidine body washes and shampoo for patient with no wounds. Clearance defined as three consecutive negative weekly swabs.</td>
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<td>Definition CDI (both phases): an episode of diarrhoea a sample of which was positive for toxin (1). No culture or typing performed.</td>
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<td>Definition of new MRSA acquisition (both phases): cases found on screening or clinical specimens taken &gt; 48 h after admission. No routine typing performed but E-MRSA 15 and 16 endemic.</td>
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</tbody>
</table>

Figure 1. Population, clinical setting, nature and timing of antibiotic prescribing and infection control interventions. ICD, infection control doctor; ICN, infection control nurse; WTE, whole time equivalent.
Population, infection control policies and resources and case definitions

Figure 1 gives details of these throughout the study, during which only the antibiotic policies (Figure 2) changed.

Rationale for the study

From September 1999, use of amoxicillin/clavulanate (an antibiotic not in the department’s antibiotic policy) had begun and become commonplace (Figure 3). This was an unplanned change in prescribing practice. The CDI rate had not increased, but in order to prevent a future rise, it was decided, in April 2001, upon routine review of the data in the audit programme, to introduce a new ‘narrow-spectrum’ antibiotic policy starting in July 2001, without knowing the data from April, May and June 2001, by which time 21 months of data would have been collected, and to evaluate its effect at the end of March 2003, after an equal period of time (21 months) had elapsed.

Intervention

The new policy (Figure 2) recommended less use of amoxicillin/clavulanate, increased use of benzyl penicillin, trimethoprim and amoxicillin and further restricting cephalosporin use. There were also prompts for the use of metronidazole, ciprofloxacin and clarithromycin, but these were not targeted for any particular change, nor were fluclrocillin, gentamicin or teicoplanin. Doctors were given a laminated pocket version of the policy to carry and continued to receive feedback, every 8–12 weeks, of individual antibiotic usage (the number of notional 7 day courses per 100 admissions per month) together with CDI rates (cases per month) and methicillin-resistant Staphylococcus aureus (MRSA) cases (per month). Antibiotic usage was fed back in this format, rather than in defined daily doses per 1000 bed days, to help doctors visualize the percentage of patients treated with individual antibiotics.

Outcomes

The primary outcome was changes in the level and linear trend of prescribing of targeted antibiotics. Changes in untargeted antibiotic use acted as an additional control, strengthening the experimental design.7,8 The secondary outcome was monthly counts of CDI, adjusted for numbers of admissions. MRSA count data (new cases) acted as an additional control, as it was thought unlikely that this would change due to the intervention.

| RTI: benzyl penicillin + trimethoprim (iv) or amoxicillin (oral or hospital acquired) |
| UTI: trimethoprin (oral/iv) or gentamicin (v. unwell) |
| Both: benzyl penicillin and trimethoprim (iv) or amoxicillin and trimethoprim (oral) |
| Septicaemia: gentamicin+amoxillicin +/-metronidazole +/-fluclrocillin |
| Cellulitis: penicillin + fluclrocillin |
| Aspiration: benzyl penicillin + metronidazole (amoxicillin + metronidazole if in hospital>1week) |

When do I use Augmentin? Severe RTI (BP low, RR >30, Moribund); second line

When do I use ciprofloxacin? Long-term catheter UTI or second line

When do I use clarithromycin? Penicillin allergy +/- or clinical suspension atypical

When do I use a cephalosporin? Microbiological advice

Figure 2. Narrow-spectrum antibiotic policy pocket card text. These details were given to all doctors on a laminated card, the first side of which gave the indications for treatment of different antibiotics and the reverse side gave doses. iv, intravenous.

Figure 3. Monthly antibiotic use (notional 7 day courses per 100 admissions) and total monthly. CDI infections before and after the intervention (July 2001).
This was an audit study and was part of the department’s clinical governance programme. Data were collected by the department’s registrars and the Royal Free NHS Trust’s Infection Control Committee. The policy of our institution is that ethical approval is not required for audit projects.

Table 1. Changes in antibiotic use after the intervention assessed using a statistical model allowing for both linear trend and level to change after the intervention antibiotic

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Baseline level</th>
<th>Initial trend</th>
<th>P value</th>
<th>Change in level after the intervention</th>
<th>P value</th>
<th>Change in trend after the intervention</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics targeted for decreased use</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>cephalosporins</td>
<td>5.63 (2.70, 8.55)</td>
<td>0.15 (−0.08, 0.37)</td>
<td>0.193</td>
<td>−3.61 (−6.47, −0.76)</td>
<td>0.015</td>
<td>−0.28 (−0.52, −0.03)</td>
<td>0.030</td>
</tr>
<tr>
<td>amoxicillin/clavulanate</td>
<td>31.03 (18.57, 43.48)</td>
<td>0.36 (−0.47, 1.18)</td>
<td>0.384</td>
<td>−13.10 (−21.87, −4.32)</td>
<td>0.004</td>
<td>−0.98 (−1.89, −0.07)</td>
<td>0.035</td>
</tr>
<tr>
<td>Antibiotics targeted for increased use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>benzyl penicillin</td>
<td>4.00 (−0.01, 8.00)</td>
<td>0.22 (−0.16, 0.60)</td>
<td>0.243</td>
<td>−4.75 (−11.66, 2.17)</td>
<td>0.173</td>
<td>0.83 (0.19, 1.47)</td>
<td>0.012</td>
</tr>
<tr>
<td>trimethoprim</td>
<td>3.47 (−0.86, 7.80)</td>
<td>0.92 (0.51, 1.34)</td>
<td>&lt;0.001</td>
<td>−5.85 (−14.49, 2.78)</td>
<td>0.187</td>
<td>−0.32 (−1.03, 0.38)</td>
<td>0.361</td>
</tr>
<tr>
<td>amoxicillin</td>
<td>18.61 (13.20, 24.02)</td>
<td>−0.08 (−0.43, 0.26)</td>
<td>0.632</td>
<td>11.21 (5.21, 17.20)</td>
<td>0.001</td>
<td>−0.24 (−0.82, 0.33)</td>
<td>0.397</td>
</tr>
<tr>
<td>Other (untargeted) antibiotics</td>
<td>44.55 (35.66, 53.44)</td>
<td>0.45 (−0.23, 1.14)</td>
<td>0.188</td>
<td>−3.08 (−16.13, 9.97)</td>
<td>0.636</td>
<td>−0.43 (−1.46, 0.60)</td>
<td>0.405</td>
</tr>
</tbody>
</table>

95% confidence intervals are given in parentheses.

*In units of 7 day courses per 100 admissions.

In units of 7 day courses per 100 admissions per month.

Potential confounders

Data were collected on the length of stay, alcohol hand-rub use and numbers of admissions, but not on bed-occupancy, staffing levels, nursing homes or patients admitted with CDI. Case mix and laboratory methods for processing specimens were unaltered. In November 2000, a ward was re-opened, explaining the rise in admissions.

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strength of the evidence by protecting the study against the
addition to the pre-intervention ‘control’ phase, increases the
control outcomes unlikely to be affected by the intervention, in
outcomes, a pre-defined endpoint, sufficient time points to allow
prescribing and the first to use feedback. It had pre-specified
controlled ITS to evaluate an intervention to change antibiotic
significant reduction in CDI. This is the first planned prospective
associated with significant changes in targeted antibiotics and a
major threats to the validity of uncontrolled ITS designs.13,17,18
This is because most other changes (such as length of stay, case
mix, seasonality, bed-occupancy, staffing levels or use of agency
staff), apart from the intervention, which could have caused
observed changes in the outcome measures, would also have
been expected to affect the control outcomes. This controlled
ITS design is therefore considered a strong quasi-experimental
design6–8,13,17,18 especially for evaluating interventions to
change antibiotic use.13 The statistical methods used and the fact
that the intervention was part of a planned study and not a
response to unusually high infection or antibiotic usage rates
protect the study against regression to mean effects, common in
ITS studies.6,8,17–19 The study design overcomes most weak-
nesses described in systematic reviews of interventions to
improve antibiotic usage4 or to reduce levels of nosocomial
infection.6,8,19–21 Its reporting is compliant with, and intended
to be an exemplar of, the consensus-agreed CONSORT equiv-
cent for infection control studies, the ORION statement
(Guidelines for Transparent Reporting of Outbreak Reports and
Intervention Studies of Nosocomial Infection).21

Although the use of additional controls excludes most poten-
tial confounders as plausible alternative explanations of the fall
in CDI, it does not exclude others, in particular, the numbers of
patients admitted with CDI from the community. This could not
be assessed, as routine microbiological data collection did not
allow differentiation of community- and hospital-acquired CDI.
However, CDI is considered largely nosocomial,1 and we were
unaware of cases admitted with CDI unattributable to a previous
admission. It was always possible to isolate cases of CDI, so an
excess of unisolated cases in the pre-intervention cannot provide
an alternative explanation for its fall in the post-intervention
phase. Although we had access to alcohol hand-rub usage,
which fluctuated at 4.5–6 mL per patient-bed-day throughout
the study, we had no data on liquid soap usage, which would be
more likely to affect CDI rates, as handwashing with soap and
water removes C. difficile spores more effectively.22 However
we do not think it likely that soap use would have risen suffi-
ciently to effect such a change in CDI rates. The study only
examined crude mortality, because of the lack of resources to
examine infection-specific mortality such as that due to respira-
ory and urinary infections. Blinded assessment of this from
notes review is hard to organize and depends on the quality of
documentation. However, departmental monthly death audits,
which independently audited the case notes of all patients who
died, did not suggest a rise in deaths from either infection, and
we think it is unlikely that this was obscured by a fall in directly
attributable deaths from CDI, as the rate of CDI itself was low.
The study is also limited by the absence of economic data, as it
did not intend to examine cost-effectiveness.

Although we are aware of one other planned prospective ITS
study12 that adequately assesses an antibiotic intervention (ward
pharmacists successfully reviewing and modifying doctors’ pre-
scriptions each day), it did not use an additional control
outcome and did not examine microbiological outcomes.
Although national guidelines unequivocally report numerous
elements of the success of restrictive antibiotic policies in redu-
cing CDI, systematic reviews5,6 show nearly all to be methodolo-
gically flawed, with only five studies of sufficient quality for
inclusion in the Cochrane systematic review of antibiotic inter-
ventions and their effect on microbiological outcomes.5,6 Only
one of these showed a reduction in CDI associated with a

Figure 4. Monthly count data for CDI, new cases of MRSA and numbers of
admissions pre- and post-intervention (July 2001).

benzyl penicillin and in sudden change for amoxicillin, which
was not reversed long term. For trimethoprim there was no
evidence of change, although there was a marked trend for
increased use before the intervention, which continued after
the intervention. Non-targeted antibiotics acted as a control and
showed no evidence of changes in either trend or level
post-intervention.

The Poisson regression showed a significant fall in CDI
associated with the intervention [IRR 0.35 (0.17, 0.73),
P = 0.009], but not in MRSA (control outcome) [0.79 (0.49,
1.28); P = 0.32] (Figures 3 and 4). Further modelling, which
allowed for exponential trends in the MRSA and CDI incidence,
again showed a significant effect on CDI (the best fitting model
showed a significant decreasing exponential trend in CDI follow-
ing the intervention, but no trend before). In contrast, there was
no decrease in level or trend for MRSA following the interven-
tion (the best fitting model showed a significant decreasing
exponential trend throughout the study, with a sudden step-wise
increase immediately following the intervention).

Crude mortality was unaltered, fluctuating randomly between
4.7% and 21% each month, with a pre- and post-intervention
mean (median) of 14.6% (14.75%) and 13.6% (14.3%) each
month. The length of stay fluctuated randomly between 11.93
and 13.53 days each month.

Discussion

The main findings of this study were that introduction of a
narrow-spectrum antibiotic policy, reinforced by feedback, was
associated with significant changes in targeted antibiotics and a
significant reduction in CDI. This is the first planned prospective
controlled ITS to evaluate an intervention to change antibiotic
prescribing and the first to use feedback. It had pre-specified
outcomes, a pre-defined endpoint, sufficient time points to allow
trend analysis, appropriate statistical analyses and consideration
of common potential confounders. In particular, the use of
control outcomes unlikely to be affected by the intervention, in
addition to the pre-intervention ‘control’ phase, increases the
strength of the evidence by protecting the study against the
Successful use of feedback to improve antibiotic prescribing and reduce CDI

significant decrease in broad-spectrum antibiotic use, including third-generation cephalosporins, although no specific data are provided on their use. The current study is therefore the best evidence to date that cephalosporin and amoxicillin/clavulanate restriction significantly reduced the use of each and the rate of CDI.

No study has adequately examined the use of feedback to change antibiotic prescribing. Our report is consistent with recent systematic reviews showing feedback helps healthcare workers adhere to clinical guidelines,9,10 a view consistent with current national recommendations,11,12 but it is not possible to tell the relative contributions of the laminated card and the feedback, although their combined use was highly effective and may provide a replicable simple intervention for acute care of the elderly units to reduce CDI rates. Given the national priority accorded to surveillance and reduction of CDI, a more virulent form of which has recently been reported,24 the findings are important.

The antibiotics chosen for the policy reflected local antibiotic susceptibilities for the main causative organisms. The use of cephalosporins in the pre-intervention phase was low compared with many hospitals, but the intervention was highly successful and might therefore be even more so in units with higher cephalosporin use.

The impact of interventions may also be dependent on the enthusiasm of local clinicians and, in this respect, the ‘pharmacist review’ method described earlier12 may be of more general use. Generalizability can only be addressed by further research. The current study design is a strong one, potentially feasible and replicable in many hospitals, which would allow synthesis of results, confirm the reproducibility of the intervention and suggest interventions worth assessing in definitive controlled trials.

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Transparency declarations

None to declare.

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