Antibiotics and hospital-acquired Clostridium difficile-associated diarrhoea: a systematic review

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CRD summary
This review investigated the association of antibiotics with hospital acquired Clostridium difficile-associated diarrhoea. Although the majority of included studies found an association with various antibiotics, antibiotic classes or components of antibiotic administration, most were limited in their ability to establish a causal relationship. The authors' cautious conclusions accurately reflect the diverse and methodologically varied nature of the evidence found.

Authors' objectives
To conduct a systematic review of epidemiological studies in order to determine the validity of reported associations of antibiotics with hospital-acquired Clostridium difficile-associated diarrhoea (CDAD).

Searching
MEDLINE (from 1966 to 2001) and EMBASE (from 1988 to 2001) were searched; some search terms were given. In addition, references were checked to identify further studies. Inclusion was limited to articles published in English, although non-English language articles found by the search were noted.

Study selection
Study designs of evaluations included in the review
The inclusion criterion was published epidemiological studies that included a comparison group without CDAD. Studies which used other CDAD cases as a comparison group (i.e. mild versus severe cases, or single versus recurrent episodes) were excluded from the review. Also excluded were case reports and descriptive studies. Included in the review were case-control studies, cross-sectional studies and cohort studies.

Specific interventions included in the review
The inclusion criterion was studies measuring the use of antibiotics. The interventions included in the review were a range of antibiotics including, but not limited to, cephalosporins, penicillin and clindamycin.

Participants included in the review
The inclusion criterion was studies of hospitalised patients. Patients with a wide range of medical conditions were included in the review.

Outcomes assessed in the review
The inclusion criterion was studies measuring an outcome of laboratory-confirmed symptomatic CDAD. Symptomatic CDAD was defined by the presence of diarrhoeal symptoms and positive results of microbiological tests of stool samples.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The studies were assessed according to the criteria of study design, selection and information bias, confounding, precision and external validity. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The data extracted included setting, comparison groups, confounding factors, and levels of exposure to antibiotics from which odds ratios (ORs) and relative risks (RRs) were calculated.

Methods of synthesis
How were the studies combined?
A brief narrative synthesis of the studies was undertaken.

How were differences between studies investigated?
Differences between the studies were discussed in the narrative synthesis, which referenced studies that had particular characteristics, with particular emphasis on factors affecting study validity.

Results of the review
Forty-eight studies were included in the review: 3 cohort studies, 23 case-control studies and 22 cross-sectional studies. It was not possible to determine the number of patients included, as details were only given of the 33 with appropriate control groups (N=10,794). A further 4 studies that met the inclusion criteria were excluded because they were not published in English.

Of the 2 studies which had the highest validity, both were cross-sectional and both found increased risks of CDAD with antibiotic exposure. One (N=347) found an RR of 2.07 (95% confidence interval, CI: 1.06, 6.62) for cephalosporin exposure for up to 1 week and an RR of 3.62 (95% CI: 1.28, 8.42) for penicillin exposure of 1 to 2 weeks, adjusted for age and severity of disease. The other larger study (N=2,671) found an OR of 4.22 (95% CI: 2.11, 8.45) for clindamycin and an OR of 1.49 (95% CI: 1.23, 1.81) for increased numbers of antibiotics, adjusted for age, length of stay and proximity to patients with CDAD.

Forty-one of the 48 studies found an increased risk of CDAD associated with antibiotic exposure in hospitals. The overall ORs ranged from 2.86 to 6.92 in 33 studies with appropriate control groups. One cohort study recorded an RR of 2.48. The ORs for specific antibiotic ranged from 2.12 to 42 for clindamycin, and from 3.84 to 26 for third-generation cephalosporins.

Authors’ conclusions
The authors’ conclusions appear to be that it is not possible to reliably answer the question of whether antibiotics are associated with CDAD because of the limited generalisability of the included studies, although the data could be interpreted as representing a general association between antibiotics and CDAD in hospitalised patients.

CRD commentary
The review question was clear and the search was adequate, although there was no attempt to identify unpublished studies; this may have led to the introduction of publication bias. In addition, the restriction of the review to articles published in English may have led to the introduction of language bias, although the authors did provide the references for relevant studies excluded for this reason. The authors did not report using methods to minimise bias and error in the validity assessment, study selection and data extraction processes. The authors carried out a validity assessment of the studies and identified the most reliable studies, which were then reported separately in the ‘Results’ section. However, they did not provide full details of how the validity assessment was conducted.

The decision to use a narrative synthesis was appropriate in view of the range of study designs, participants and antibiotics included in the review. The narrative synthesis was brief, but was supported by the use of study tables. However, these only included the 33 studies which were judged to have used appropriate comparison groups. The authors’ conclusions accurately reflect the diverse and methodologically varied nature of the evidence found, and their recommendations are appropriately cautious.
Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that future studies need to be aware of epidemiological principles, in particular the need for appropriate controls, adequate sample size, minimisation of bias and the control of confounding factors.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.