Comparative effectiveness of Clostridium difficile treatments: a systematic review

Drekonja DM, Butler M, MacDonald R, Bliss D, Filice GA, Rector TS, Wilt TJ

CRD summary
This review compared the effectiveness and harms of antibiotic treatments in adult patients with Clostridium difficile infection. The authors concluded that no antimicrobial agent was clearly superior for initial cure and recurrence was less frequent with fidaxomicin than vancomycin. The suboptimal quality of studies, small sample sizes and variable study characteristics suggest that the cautious conclusion is justified.

Authors' objectives
To compare the effectiveness and harms of different antibiotic treatments in adult patients with Clostridium difficile (C. difficile).

Searching
MEDLINE, AMED, The Cochrane Library and ClinicalTrials.gov were searched from inception to August 2011. The search strategy was presented. Additional material was sought from bibliographies, United States Food and Drug Administration website and through contact with experts. The search was limited to articles in English.

Study selection
Randomised controlled trials (RCTs) of adult patients with C. difficile infection who received treatments available in USA and observational studies that reported on disease severity or strain were eligible for inclusion. Outcomes of interest were initial cure and recurrence (definitions as reported in the studies) and treatment harms. Studies were excluded where they were presented only at professional meetings.

Just over half of the included studies were conducted in USA; there was one UK study. Definition of C. difficile varied. Most studies compared different antimicrobial agents at various doses. Other comparisons included the same drug at different doses, combination drugs and placebo. Included treatments were vancomycin (the most frequently studied), metronidazole, bacitracin, nitazoxanide, fidaxomicin and rifampin/metronidazole. In-patients and outpatients were included. Reported mean ages ranged from 42 to 69 years. One study included an infant.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Trial quality was assessed for allocation concealment, blinding and use of intention-to-treat (ITT) analysis. There was no reported assessment of observational studies.

Two reviewers independently assessed the trials for methodological quality.

Data extraction
Data were extracted on the outcomes of interest, which included initial cure, recurrence, duration of diarrhoea and mortality. Data on clearance of organism or toxin were extracted. Risk ratios (RR) and 95% confidence intervals (CI) were presented. Where possible, ITT data were used.

Two reviewers independently extracted the data.

Methods of synthesis
A narrative synthesis was presented. Study differences were presented in tables.

Results of the review
Eleven RCTs (1,463 participants; 1,324 ITT analysis) and two observational studies were included. Around one half of the RCTs reported adequate allocation concealment and blinding (five were double-blind) and around one quarter presented ITT analysis.
Vancomycin compared with metronidazole (three trials): Initial cure rate ranged from 84% to 94% for vancomycin and 73% to 94% for metronidazole. Recurrence ranged from 7% to 17% for vancomycin and 5% to 17% for metronidazole. There were no statistically significant differences between treatments. There was insufficient evidence for the impact of disease severity on outcomes.

Metronidazole or vancomycin compared with other agents (eight trials): One small trial (21 participants) that compared vancomycin with placebo found a statistically significant difference in initial cure rate (75% versus 11%). Fidaxomicin was significantly more effective than vancomycin for lower recurrence (15% versus 25%). Vancomycin was favoured over bacitracin in terms of clearance of toxin (RR 1.68, 95% CI 1.14 to 2.47; two trials) and viable C. difficile organisms (RR 1.67, 95% CI 1.12 to 2.49; two trials). These outcomes were also statistically significant when vancomycin was compared to placebo for clearance of toxin (RR 2.75, 95% CI 1.17 to 6.44) and organism (RR 8.25, 95% CI 1.29 to 52.77).

Mortality was rare. There were no statistical differences between treatments for duration of diarrhoea and (where reported) adverse events.

Cost information
Cost data were presented for the various included drugs. These ranged from US dollars ($) 20.70 (metronidazole, flagyl) to $3,360 (fidaxomicin, dificid) for a 10-day course of treatment.

Authors' conclusions
No antimicrobial agent was clearly superior for the initial cure of C. difficile infection. Recurrence was less frequent with fidaxomicin than with vancomycin.

CRD commentary
The research question was clear. Inclusion criteria were sufficiently detailed to enable replication. The chosen data sources appeared relevant to the topic area. The review relied upon studies in English and potentially relevant studies in other languages might have been overlooked; the extent to which this might have impacted on the reliability of a review that focused on drugs available only in USA was unclear. Study characteristics were presented clearly, but full statistical data were lacking on some outcomes. The review process was conducted with sufficient attempts to minimise error and bias. Appropriate quality assessment criteria were applied.

The suboptimal quality of studies, together with small sample sizes and highly variable study characteristics (acknowledged by the authors), suggest that the author's cautious conclusion is justified.

Implications of the review for practice and research
The authors did not state any implications for research or practice.

Funding
Agency for Healthcare Research and Quality, United States Department of Health and Human Services.

Bibliographic details

PubMedID
22184691

Linked records
- Effectiveness of early diagnosis, prevention, and treatment of Clostridium difficile infection

DOI

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Aminoglycosides /therapeutic use; Anti-Bacterial Agents /therapeutic use; Clostridium Infections /drug therapy /microbiology /mortality; Clostridium difficile; Comparative Effectiveness Research; Diarrhea /drug therapy /microbiology; Drug Therapy, Combination; Humans; Metronidazole /therapeutic use; Recurrence; Vancomycin /therapeutic use

**AccessionNumber**
1201200005

**Date bibliographic record published**
20/01/2012

**Date abstract record published**
22/01/2012

**Record Status**
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.