Antimicrobial prophylaxis for urinary tract infection in persons with spinal cord dysfunction


Authors' objectives
To assess the benefits and harms of antimicrobial prophylaxis to prevent urinary tract infections (UTIs) in persons with neurogenic bladders caused by spinal cord dysfunction.

Searching
MEDLINE from 1966 to January 1998, and EMBASE from 1974 to January 1998, were searched using the following search terms: 'urinary tract', 'urinary tract infections', 'bacteriuria', 'paraplegia', 'quadriplegia', 'spinal cord injuries', 'multiple sclerosis', 'neurogenic bladder' and 'neuropathic bladder' (free text term). Case reports and studies of animals were excluded. CINAHL was also searched from 1982 to July 1998 using analogous terms. No language restrictions were applied in any search and 'grey' literature, such as letters and conference abstracts, was not excluded. Additional articles were identified by contacting experts and by reviewing the reference lists of articles obtained from the searches. The authors also queried experts about possible unpublished studies, but none were identified.

Study selection
Study designs of evaluations included in the review
Controlled trials were included.

Specific interventions included in the review
Only studies that looked at antimicrobial prophylaxis of UTI were considered for inclusion. The treatments compared were any antimicrobial versus no antimicrobial, and a specific antimicrobial versus no antimicrobial. The antimicrobials included nitrofurantoin (50 to 100 mg, or 25 mg for children weighing less than 25 kg), methenamine (hippurate 1 g or mandelate 2 g), trimethoprim (40 to 160 mg), sulfamethoxazole (200 to 800 mg) and ciprofloxacin (100 mg). Where reported, the average duration of treatment ranged from 50 days to 7 months for acute, and from 21 days to 11 months for nonacute.

Participants included in the review
Adults or adolescents who had neurogenic bladder due to spinal cord dysfunction were included. Studies that included children under the age of 13 years were excluded.

Outcomes assessed in the review
Only studies that include bacteriuria or UTI were considered for inclusion. The main analysis outcomes were asymptomatic infections (also called asymptomatic bacteriuria, colonisation or laboratory infection) and symptomatic infection UTI.

How were decisions on the relevance of primary studies made?
Studies with potentially relevant titles had their abstracts reviewed. The full article was reviewed for those studies with potentially relevant abstracts, whilst for those without abstracts, the full article was retrieved. Title and abstract reviews were conducted independently by two physicians, and any disagreements were resolved by consensus or by one or two senior clinician researchers. Translators were available for foreign language articles.

Assessment of study quality
Validity was assessed using the quality criteria developed by Jadad et al. and Schulz et al. (see Other Publications of Related Interest nos.1-2, respectively). The Jadad criteria assess details of blinding and randomisation, and accounting for patient drop-outs, on a scale of 0 (lowest) to 5 (highest). The Schulz criterion assesses whether a study adequately conceals allocation. The studies were graded by one reviewer. Questions about scoring particular items were resolved in consultation with Jadad.
Data extraction
Two reviewers independently abstracted the data, and any disagreements were resolved by consensus. The authors tried to clarify study design, patient population, and data issues for five studies, and were successful in obtaining additional data from two investigators. The authors were only able to obtain data stratified by study phase for one crossover study. For the remaining three crossover studies they used complete data, which aggregated the results across both study phases.

The presence of clinical heterogeneity meant that trials involving acute spinal cord injury patients (less than 90 days post-injury) were considered separately from those of nonacute spinal cord injury patients, and from those with other chronic conditions associated with spinal dysfunction.

The weekly infection rate was used as the common statistic. When the differences between the treatment and control were statistically significant, the authors calculated the number of weeks of treatment needed to prevent one infection. To compute standard errors, the authors used the patient sample size as opposed to the number of cultures. To avoid double-counting the control groups for studies that had more than one comparison, the authors generally chose the most clinically relevant comparison; the exception was one study for which a summary statistic combining all relevant treatment results was produced, using weights equal to the treatment group sample sizes.

Methods of synthesis
How were the studies combined?
The random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.3) was used to pool the effect sizes. Publication bias was assessed using a funnel plot.

How were differences between studies investigated?
A chi-squared test was used to assess statistical heterogeneity. The results of the individual studies were presented in forest plots, which were ordered by Q score and alphabetically for studies with the same score.

Some sources of heterogeneity were identified and built into predefined subgroup analyses. Sensitivity analyses were used to explore additional sources of clinical heterogeneity, not built into the predefined subgroup analyses, and the variability in study quality. For the latter, the studies were stratified into those with a quality score of at least 3 versus those with a score of 2 or less.

Results of the review
Fifteen trials with 883 participants were included in the review: 8 studies (n=510) included acute patients while 7 (n=373) included nonacute patients.

Only 2 studies used an appropriate concealment of allocation. The quality score ranged from 1 to 5 (median: 1) for acute patients, and from 0 to 5 (median: 4) for nonacute patients.

Any antimicrobial versus no antimicrobial.

There was no significant reduction in the symptomatic infections for either acute (3 studies) or nonacute (4 studies) patients (P>0.05), and the chi-squared test for heterogeneity did not reject either type of patient (P=0.85 and P=0.71, respectively). The estimated pooled difference in weekly infection rates between the treatment and control groups for both patient types was -0.04.

The pooled difference in asymptomatic bacteriuria rates for acute patients (7 studies) was -0.27 (95% confidence interval: -0.14, 0.15, P<0.05). This value indicated that one patient would require 3.7 weeks of treatment on average to prevent one asymptomatic infection. For nonacute patients (6 studies), the reduction approached statistical significance (P=0.06).

A funnel plot of the comparisons did not support the existence of publication bias. This conclusion must be regarded as tentative given the small number of studies.
The sensitivity analysis of the population (control group) infection rates indicated heterogeneity in the asymptomatic strata for both acute and nonacute patients. In the acute stratum, one study had a relatively low population infection rate, and by omitting organisms within the species Pseudomonas, it used a different outcome definition than the other studies. Removing this study eliminated statistical heterogeneity in the population infection rates (chi-squared \( P=0.46 \)) and did not change the pooled results. In the nonacute stratum, further analyses neither elucidated the possible reasons for heterogeneity nor indicated additional subgroup analyses to perform.

Prophylaxis (other than with methenamine) resulted in an approximately two-fold increase in the proportion of antimicrobial-resistant bacteria cultured from patients.

**Authors’ conclusions**
The regular use of antimicrobial prophylaxis for most patients who have neurogenic bladder caused by spinal cord dysfunction was not supported. A clinically important effect, however, has not been excluded. Future research should focus on randomised trials in those patients who have recurrent UTIs that limit their daily functioning and well-being.

**CRD commentary**
This appears to have been a well-conducted review. The aims were clearly stated and the inclusion and exclusion criteria were defined. A comprehensive literature search was undertaken, and experts in the field were contacted in an attempt to identify any unpublished studies. Publication bias was investigated using a funnel plot. A systematic procedure involving one or more reviewers was used to assess the relevancy of the retrieved articles and data extraction. The authors also assessed the validity of the included trials. Relevant details of the included studies were tabulated clearly and were described in the text. Some sources of clinical heterogeneity were taken into account using predefined subgroup analyses. Differences between the included studies were assessed statistically using a chi-squared test and sensitivity analysis. The results of the individual studies were pooled, despite the presence of heterogeneity. The presence of heterogeneity means that you are less certain about your pooled estimate, which is reflected in the 95% confidence interval. The authors acknowledged that further sources of heterogeneity might exist, and that further subgroup analyses could have been explored but were not feasible in this review.

The authors' conclusions follow from the results.

**Implications of the review for practice and research**
Practice: The authors state that the routine use of antimicrobial prophylaxis for the general population of persons with spinal cord dysfunction is not recommended, owing to the doubling of resistant organisms and the evidence in this review.

Research: The authors state that future research should focus on randomised trials in those patients who have recurrent UTIs that limit their daily functioning and well-being.

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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.