Systemic colistin use in children without cystic fibrosis: a systematic review of the literature
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CRD summary
The review concluded that available evidence, mainly from old case series, suggested that systemic colistin was effective, and had an acceptable safety profile, for treatment of children without cystic fibrosis who have had multi-drug resistant Gram-negative bacterial infections. The limitations of the review, with respect to study quality and evidence, make the reliability of the authors' conclusions unclear.

Authors' objectives
To evaluate the safety and effectiveness of the prophylactic use of systemic colistin in the treatment or prevention of infection in children without cystic fibrosis.

Searching
PubMed, Scopus and the Cochrane Library, were searched from approximately 1950 to July/September 2008 for publications in English, Spanish, French, German, Italian or Greek. Search terms were reported. Bibliographies of each retrieved article were handsearched. Conference abstracts were excluded.

Study selection
Studies evaluating the use of intravenous, intrathecal, intramuscular, or intraventricular colistin for the treatment or prophylaxis of infection by colistin-susceptible pathogens in paediatric patients, where the majority of patients did not have cystic fibrosis, were eligible for inclusion. The review assessed clinical outcomes defined as the outcome of the index infection for which colistin treatment was started and adverse events.

The included studies were either case series or case reports. The majority of included studies were of treatment of infections by colistin; two case series were of surgical prophylaxis or prophylaxis in burns patients; the children in three of the case reports had no underlying disease. Most of the included studies used intravenous or intramuscular colistin and the dosage varied significantly. In the included studies, penicillins were the most common antimicrobial agents used concomitantly with colistin. The age of the children in the included studies ranged from newborn and premature to 19 years.

The underlying diseases in the included studies were very varied: burns; hydrocephalus plus parkinsonism/ventriculoperitoneal shunt plus stereotaxic surgery; head injury; acute lymphocytic or myelocytic leukaemia; congenital meningomyelocele; maternal infection; prolonged rupture of foetal membranes; respiratory distress syndrome; central nervous system injury; erythroblastosis foetalis; major congenital anomaly; upper respiratory tract infection; none; or not reported.

The Gram-negative bacterial pathogens isolated in the included studies were: Pseudomonas aeruginosa, Klebsiella pneumoniae, Aerobacter aerogenes, Acinetobacter baumannii, Haemophilus influenzae, Edwardsiella tarda or Escherichia coli. The included studies reported the following outcomes: cure from infection; improvement; deterioration; or death.

The authors did not state how many reviewers were involved in study selection, or how the papers were selected for the review.

Assessment of study quality
The authors did not report conducting a formal validity assessment. However, it appeared that they assessed: appropriateness of dosage; whether there was sufficient detail on the participants and their underlying diseases; concomitant treatment; and losses to follow-up.

Data extraction
The data extracted included: the number and underlying diseases of the included children; concomitant treatment to colistin; the characteristics of the infection (type, causative pathogen and site of isolation); antibiotic treatment prior to
colistin use; the clinical outcome for each patient; and reported adverse events.

Two reviewers independently performed the data extraction.

**Methods of synthesis**
The numbers of events for case series were calculated related to whether colistin was given for prophylaxis or to treat infection. A summary of the results was then presented and no further analysis was performed.

**Results of the review**
Twenty five relevant studies (n=370 children) were identified, including ten case series (n=355 children) and fifteen case reports (n=15 children).

**Colistin usage for treatment of bacterial infections** (nine case series; n=311 patients): Over all the case series, 86.7% of children were reported as cured, 3.7% as improved, 2.2% as deteriorated and 7.4% died. Most (70%) of deaths were attributable to infection, 20% to other pathologies, and 10% to superinfections or intercurrent infections. Adverse effects for nephrotoxicity in these children were: 10.6% with cylindruria (urine casts) or haematuria; 2.6% with elevated blood urea nitrogen of more than 10%, 1.6% with renal tubular cells in urine, 1% with proteinuria, and 0.6% children with a significant increase in serum creatinine. Other adverse events were reported in 2.6% of children. No neurotoxicity was reported.

**Colistin usage for prophylaxis** (two case series; n=44 patients): No incidence of infection in any of the children was reported. Deaths (20.5%) were attributed to the underlying pathologies of the children, with no signs of colistin-related toxicity reported in the biopsies performed. The reported adverse effects for these children were 36.4% with renal tubular cells in their urine and 31.8% had proteinuria. The remaining children (29.5%) had no adverse effects.

For all the case series, the authors reported that nephrotoxicity occurred in 10 of the 355 children (2.8%). This number was presumably derived by adding together the eight children with elevated blood urea nitrogen of more than 10 and the two children who had a significant increase in serum creatinine.

Data from case reports was also reported.

**Authors' conclusions**
The available evidence, mainly from old case series, suggested that systemic colistin was an effective and acceptably safe treatment of children without cystic fibrosis who have had multi-drug resistant Gram-negative bacterial infections.

**CRD commentary**
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched but unpublished studies were not considered. Attempts were made to reduce language bias. Publication bias was not assessed. Study quality was not assessed as only case series and case reports were included, but flaws in individual studies were identified. It was not clear what overall efforts had been taken in the review to reduce error and bias, but data extraction was carried out independently by two reviewers. Relevant study details were reported. No statistical analysis was performed, so statistical heterogeneity was not assessed.

The authors highlighted the fact that most of the studies identified were older studies published before 1977 (most of the case series before 1972), and that the use of colistin had reduced after concern about nephrotoxicity in the 1970s. Since most of the studies were old, the relevance of the review findings to current clinical practice is uncertain. The authors comment that nephrotoxicity occurred in 2.8% of the children in the case series, which may have been an underestimate in view of the number reported in the case reports.

In view of some potential limitations arising from the review process, uncertainties about the quality of included studies, and reservations about the safety of the interventions, the extent to which the authors’ conclusions are reliable is unclear.

One author had received speaker honoraria from several drug companies.
Implications of the review for practice and research

Practice: The authors stated that more recent studies have shown that colistin appears to have lower toxicity (specifically nephrotoxicity) than older studies in the 1960s and 1970s implied, and that colistin may therefore be useful in the treatment of children with multi-resistant Gram-negative infections. There has been confusion about the dosage of colistin in the past which has led to overdosage. The recommended dosage is a total daily dose of 50,000 to 75,000 International Units (IU) per kg for adults and children with a body weight of less than 60kg, administered three times daily. Drug absorption and clearance differ between children and adults and adjustment for body weight is essential. The authors also recommend further adjustment of colistin dosage when there is impaired renal function, and for critically ill or immunocompromised children, but that suboptimal dosage may lead to resistance.

Research: The authors did not state any implications for research.

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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.