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(Accepted 23 November 2004)

Evidence based case report

Use of antibiotics in suspected haemolytic-uraemic syndrome

Bob Phillips, Kay Tyerman, Simon M Whiteley

An 11 year old girl was admitted to our specialist paediatric intensive care unit under the joint care of paediatric intensivists and nephrologists. She had presented to her local hospital with a four day history of vomiting, diarrhoea, and becoming progressively more unwell. Initial blood tests showed acute renal failure and thrombocytopenia. We tentatively diagnosed haemolytic uraemic syndrome, although sepsis with renal dysfunction was part of the differential. These uncertainties arose because her blood film was not typical of haemolytic uraemic syndrome, she had a clotting abnormality, and we had no microbiological confirmation. Treatment with broad spectrum antibiotics was proposed. Some doubt remained about this treatment, however, because of a well publicised study suggesting that giving antibiotics to patients with *Escherichia coli* 0157:H7 enteritis could worsen haemolytic uraemic syndrome. We used a five step evidence based approach to address this problem.

Formulate the question

The first step in our approach was to formulate an answerable clinical question: In children with suspected haemolytic uraemic syndrome, particularly associated with *E coli* 0157:H7 infection, does treatment with antibiotics lead to increased morbidity, particularly progressive haemolytic uraemic syndrome or sepsis, compared with withholding antibiotics?

Acquire some information

Ideally this question would be answered by large randomised controlled trials. If trials were absent or inadequate, cohort studies or well conducted case-control reports would be helpful. As systematic reviews are increasingly used in all areas of research (not just randomised controlled trials) we looked first for such reports. Not expecting to find randomised controlled trials, we looked for studies using the PubMed clinical queries systematic review filter rather than the Cochrane Library. The search terms "hemolytic uremic syndrome AND antibiotics" returned three citations.

Only one of these was a relevant systematic review of trials and observational studies.¹ As this was published in 2002, we searched for more recent relevant individual studies and found none.

Appraise the evidence

We used a combination of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) proposal² and the Grading of Recommendations Assessment Development and Evaluation (GRADE) Working Group approach³ to appraise and summarise the information. The MOOSE proposal sets out criteria for the effective reporting of meta-analysis in observational studies. The GRADE group is an international collaboration of clinicians and epidemiologists involved in the development of a unified system to support clinical practice recommendations.

The authors of the systematic review searched electronic databases, reference lists, and an ongoing trials database and consulted relevant experts to discover any rigorous study looking at the association between *E coli* 0157:H7 enteritis, antibiotic use, and development of haemolytic uraemic syndrome.¹ Studies were independently abstracted, and the reviewers used predetermined appraisal criteria. The results were pooled by using a fixed effects model, a funnel plot showed no asymmetry, and heterogeneity was appropriately explored.

The results of the review are summarised in the GRADE evidence profile (tables 1 and 2). The studies, which included two small randomised

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BMJ 2005;330:409-10

Table 1 Quality assessment of trials in systematic review for outcome development of haemolytic uraemic syndrome¹

No of studies comparing antibiotics with no antibiotics	Design	Limitations	Consistency	Directness	Other modifiers
10	2 RCT, 3 cohort, 5 case-control	No serious limitations	Inconsistent*	Direct	Possible publication bias*

*Results of two studies were greatly different from the other eight, showing increased likelihood of haemolytic uraemic syndrome with antibiotics. When these were removed, there was no heterogeneity. This could be due to reverse publication bias.

Table 2 Summary of findings of systematic review of studies comparing antibiotic treatment with no antibiotics for the outcome development of haemolytic uraemic syndrome¹

Median % of patients with syndrome (range)	Total No of patients *	Risk of haemolytic uraemic syndrome		Quality of studies	Importance
		Relative (95% CI)	Absolute (range)		
13 (12-14)	688	1.15 (0.79 to 1.68)	2 cases/100 treated (7 to -2)	Low	High

*In cohort studies.

controlled trials, were overall of low quality. The confidence interval around the pooled odds ratio for development of haemolytic uraemic syndrome with antibiotics included 1, indicating no clear effect of antibiotics. The width of the confidence interval is consistent with either moderate harm or moderate benefit.

Apply the answer

The combination of uncertainties in this case is important. Our patient was not in the typical age range, she did not have the typical haematological picture for *E coli* haemolytic uraemic syndrome, and she was critically ill. Various other organisms can produce haemolytic uraemic syndrome as part of a septic illness.⁴ The clinical balance was between leaving untreated (for example) pneumococcal sepsis and worsening an *E coli* 0157:H7 enteritis by giving antibiotics. The evidence we found highlighted the paucity of clinical evidence indicating harm from treating children with *E coli* enteritis compared with the overwhelming clinical experience regarding the use of antibiotics in sepsis.⁵ We concluded that the perceived benefit of treating sepsis in this complex atypical patient outweighed the potential harm if *E coli* 0157:H7 enteritis was the underlying problem. If the child had presented with the typical picture of haemolytic uraemic syndrome the lack of benefits of antibiotics would have swayed us against using them

Assess the outcome

Our patient deteriorated after admission to intensive care and required ventilation for a low conscious level. She was treated with broad spectrum antibiotics. Two days later serology indicated an *E coli* 0157:H7 infection, which was subsequently confirmed from stool samples. Antibiotics did not seem to worsen her haemolysis or her acute renal impairment. In total, she was anuric for 6 days and required dialysis for 10 days. At her six week outpatient review she was normotensive with a serum creatinine concentration of 56 µmol/l and persistent proteinuria. Ongoing proteinuria and evidence of renal impairment after a year would put her into higher risk group for long term renal complications, and she remains under renal review.

Contributors: BP phrased the question, performed the searches and initial appraisals, and wrote the draft. KT and SMW both reviewed the searches, studies and appraisal and helped write the final article. BP will act as guarantor.

Competing interests: BP is a member of the GRADE Working Group and is working to promote its use in applying evidence in clinical practice. He will not gain financially from its promotion or use.

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