in a real life situation, where wet combing is performed by parents who have not received prior training or supervision, this might not be as successful.

In conclusion, there is some evidence that wet combing is an effective treatment for pediculosis capitis when used correctly and consistently. However, as outlined above, the currently existing evidence has considerable limitations. A sufficiently large, well conducted randomised controlled trial with adequate randomisation process and appropriate allocation concealment would therefore be desirable.

However, wet combing it is not associated with any potential side effects and is generally preferred by parents over treatment with insecticides. In view of the rising level of resistance of *Pediculus humanus capitis* this method may represent a viable alternative, particularly as treatment failure does ultimately not carry the risk of having detrimental effects to the child's health.

CLINICAL BOTTOM LINE

- There is limited evidence that suggests that wet combing is an effective treatment for pediculosis capitis, although cure rates are variable. (Grade B)
- Parents prefer this treatment option over that of pediculocides. (Grade D)
- Treatment for a longer duration than the generally recommended 2 weeks may improve success rates. (Grade D)

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Leukocytosis as a predictor for progression to haemolytic uraemic syndrome in *Escherichia coli* O157:H7 infection

Report by

M A Anjay, Specialist Registrar in Paediatrics, James Paget University Hospitals NHS Foundation Trust, Lowestoft Road, Gorleston, Great Yarmouth, Norfolk NR31 6LA, UK; anjayma@gmail.com

P Anoop, Paediatric Haemato-oncology, Royal Marsden Hospital, Surrey, UK

A Britland, Airedale General Hospital, Keighley, West Yorkshire, UK

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You are the specialist registrar in paediatrics doing the ward rounds. There has been a recent outbreak of *Escherichia coli* (*E coli*) O157:H7 gastroenteritis in the community. A 5-year old girl was admitted 3 days ago with bloody diarrhoea, abdominal cramps and vomiting. Her stool has grown *E coli* O157:H7. She is now stable and her parents are keen to take her home but are understandably anxious and ask you about possible complications. You are aware of the risk for progression to haemolytic uraemic syndrome (HUS). However, you are not sure if all such patients should be closely monitored. You note that the patient now has a normal platelet count and renal function and wonder if there are any simple parameters to predict the risk of HUS, which may take up to 2 weeks to develop.

You talk to the consultant in public health medicine, who kindly directs to you to the national guidelines by the Health Protection Agency (HPA) on the management of *E coli* O157:H7 infections.¹ Unfortunately, the guidelines do not answer your question. Your consultant has come across anecdotal evidence that leukocytosis may be a predictor for HUS in such children.

You decide to do a literature search and critically appraise the evidence.

Structured clinical question

In a child with *Escherichia coli* O157:H7 infection [patient], does a high white blood cell count [risk factor] predict progression to haemolytic uraemic syndrome [outcome]?

Search strategy

Secondary sources

Cochrane library, Best Evidence, Clinical Evidence

No relevant articles were found

Primary sources

MEDLINE (1966 to date) and OLDMEDLINE (1950–1965) searched by the PubMed interface on 29/10/2006.

Search terms

“Hemolytic uremic syndrome” AND “*Escherichia coli* O157” with limits (English, Human, All child: 0–18 years) revealed 267 results.

Addition of the key words (leukocytosis OR “white cell count”) to the above yielded only seven results. This was felt to be an inappropriately low number, possibly due to variations in the terms used by authors (“elevated WBC”, “high leukocytes”, “increased white cell count”, etc).

Table 2 Leukocytosis as a predictor for progression to haemolytic uraemic syndrome

Citation	Study population	Study type	Risk factor	Outcome	Results (95% CI)	Comments
Tserenpuntsag <i>et al</i> , 2005 (USA) ²	Hospitalised patients with confirmed <i>E coli</i> O157 infection, 238 with full case notes included, 1998–99	Case control study (level 3b)	WBC $>13 \times 10^9/l$	Confirmed or probable HUS	$p < 0.001$ Adjusted OR 4.4 (1.6 to 12.6)	Sound methodology. Clear definitions for “confirmed” and “probable” cases. Confounding variables accounted for. However, study also included adults.
Wood <i>et al</i> , 2001 (Scotland) ³	170 confirmed or probable <i>E coli</i> O157:H7 infections from Central Scotland outbreak of 1996 monitored in community	Prospective cohort study (level 2b)	WBC $>$ upper limit for age (reference ranges from local laboratory)	Confirmed HUS	Sensitivity 88.9% (51.8 to 99.7) Specificity 79.2% (74.1 to 84.4) Negative predictive value 99.5% (97.1 to 100)	Strict exclusion criteria, well validated data. Patients with severe initial presentation needing hospitalisation excluded. Proportion of children in sample size not clear. Concludes absence of leukocytosis indicates very low risk for HUS. Relative risk for absolute WBC counts not provided.
Dundas <i>et al</i> , 2001 (Scotland) ⁴	120 hospitalised patients with <i>E coli</i> O157:H7 from Central Scotland outbreak of 1996	Case control study (level 3b)	WBC $>20 \times 10^9/l$	Confirmed HUS	OR 8.3 (1.1 to 60.3)	Strict exclusion criteria. Confounding variables not fully explained. Study also included adults. Possible overlap with Wood <i>et al</i> 's paper on the same outbreak. Gives separate data for neutrophils. Wide confidence intervals for risk.
Ikeda <i>et al</i> , 2000 (Japan) ⁵	288 inpatient school children in the 1996 Sakai outbreak in Japan	Case-control study (level 3b)	WBC $>11 \times 10^9/l$	Confirmed HUS	OR 5.03 (2.13 to 11.87)	Exclusively paediatric study. Confounding factors not clear. High CRP also noted to be significant. “Incomplete” HUS excluded from final analysis. Postulates a “predictor index scoring system” based on WBC count, CRP and temperature.
Buteau <i>et al</i> , 2000 (Canada) ⁶	All children <18 years with culture-proved sporadic <i>E coli</i> O157:H7 infections seen at Sainte-Justine Hospital 1987–1997	Retrospective cohort study (level 2b)	WBC $>11 \times 10^9/l$	Confirmed HUS	RR 3.8 (1.5 to 9.7) $p < 0.002$	Excellent methodology. Large focussed study looking at leukocytosis. Rigid validation criteria. Clear progressive association of HUS with rising WBC count.
Wong <i>et al</i> , 2000 (USA) ⁷	Cohort of 71 children <10 years with <i>E coli</i> O157 positive stool cultures	Prospective cohort study (level 2b)	WBC $>13 \times 10^9/l$	Confirmed HUS	Adjusted RR 6 (1.2 to 29.8) $p < 0.03$	Exclusive paediatric study with sound methodology, strict inclusion criteria and clear definitions. Main aim of the study was to evaluate antibiotic-associated risk.
Kawamura <i>et al</i> , 1999 (Japan) ⁸	126 junior high school children with proven <i>E coli</i> O157:H7 infection in the 1996 Sakai outbreak	Prospective cohort study (level 4)	WBC $>10 \times 10^9/l$	Confirmed HUS	34% of patients with WBC above cut-off level of $10 \times 10^9/l$ developed HUS. Significant difference in median, minimum and maximum WBC counts among the two groups	Conclusions are based on imperfect statistical analysis. Risk not quantified and confidence limits not provided. Both high WBC and elevated CRP identified as independent risk factors.
Bell <i>et al</i> , 1997 (USA) ⁹	278 Washington State children <16 years with symptomatic confirmed <i>E coli</i> O157:H7 infection during a large 1993 outbreak	Retrospective cohort study (level 2b)	WBC $>13 \times 10^9/l$	“Complete” and “incomplete” HUS	RR 7.2 (2.8 to 18.5)	Extensive study with good methodology. Concludes that leukocytosis will identify 72% of children who will develop HUS.
Akashi <i>et al</i> , 1994 (Japan) ¹⁰	42 nursery school children with confirmed <i>E coli</i> O157:H7 infection in the 1990 Saitama epidemic	Prospective study (level 4)	Absolute WBC cut-off count not defined. “Rising” WBC count implicated as a risk factor.	“Confirmed” and “incomplete” HUS	Significant differences in WBC count ($p < 0.05$) on “day 4” of illness	Asymptomatic children were also included by screening. Final analysis also included ‘incomplete’ HUS. Study grossly handicapped by lack of clear data and insufficient statistical analysis.
Pavia <i>et al</i> , 1990 (USA) ¹¹	20 residents with <i>E coli</i> O157:H7 from two institutions for mentally retarded children in Utah; 13 culture confirmed	Case control study (level 4)	Elevated WBC count (median count among cases $23.7 \times 10^9/l$)	Confirmed HUS	Median WBC count cases vs controls $23.7 \times 10^9/l$ vs $9.1 \times 10^9/l$, $p = 0.018$	Also included unconfirmed cases of possible <i>E coli</i> infection. Limited size of “case” and “control” population. Odds ratio and confidence limits are not provided.

A wider final search strategy adding suitable new key words to the original search was attempted as follows: ("Hemolytic uremic syndrome" AND "*Escherichia coli* O157") AND (risk OR predictors).

This resulted in 71 hits. Among these, no systematic reviews relevant to the clinical question could be identified. Ten articles were found to be of relevance.²⁻¹¹ See table 2.

Commentary

E coli O157:H7 is a relatively uncommon cause of infectious gastroenteritis in children. However, the severity of symptoms, the possibility of outbreaks and the potential for severe complications means it is of considerable public health importance. Infections with this subtype are known to lead to HUS in 2-7% of overall cases, which may rise to 30% in outbreaks.¹²⁻¹³ The disease can be particularly severe in children, with reported case fatality rates of 3-17% and a significant incidence of long-term sequelae in survivors.¹⁴

Since more than 90% of children with *E coli* O157:H7 infection do not progress to HUS, intensive clinical and/or laboratory monitoring of all cases may not be feasible or cost-effective. Attempts have been made to set up monitoring protocols to identify high-risk patients and help with early interventions.³ As the median time for development of HUS is 9 days (range 1-15 days), early identification of risk factors will enable triage into high- and low-risk groups and help target interventions appropriately.

Identification of clinical risk factors including the intensity of fever, vomiting, duration of illness and presence of blood in stools has been attempted with limited success.⁵⁻⁷ More recent efforts have focussed on objective laboratory criteria such as raised inflammatory markers, low serum protein, elevated lactate dehydrogenase levels and albuminuria.³⁻⁴ An elevated white blood cell (WBC) count has been noted to be associated with a higher risk for HUS, with some authors claiming a sensitivity and specificity of around 90%.³

Being a rare complication of an uncommon infection, case-control studies may be appropriate to define risk in this clinical situation.² However, clustering of a large number of cases during epidemics may enable cohort studies to be performed with relative ease.³⁻⁵⁻⁹ Most authors in our analysis have identified *E coli* infection on the basis of positive stool cultures and some have also used seropositivity and/or clinical diagnosis.³⁻⁹ In all the above studies, the use of standardised criteria has made the diagnosis of HUS unambiguous. Attempts by some authors to subclassify HUS into confirmed/complete and probable/incomplete forms has only academic relevance and does not affect the validity of the conclusions.²⁻⁹ The relatively short time period between exposure and outcome as well as the serious nature of the condition requiring hospitalisation have ensured accurate data collection as well as lack of attrition in all studies.

Leukocytosis has consistently been noted as significant by several authors in their attempts to identify clinical, laboratory and medication-related risk factors for progression to HUS.²⁻¹¹ A comprehensive and focussed study by Buteau *et al* has demonstrated a clear progressive association of HUS with a rising WBC count.⁶ Two well conducted studies by Tserenpuntsag *et al* and Bell *et al* have clearly defined the high risk associated with a WBC count of $>13 \times 10^9/l$ even though the former study included adults as well.²⁻⁹ Similar results have also been obtained by Dundas *et al*, Ikeda *et al* and Wong *et al*, albeit at different WBC cut-off levels.⁴⁻⁵⁻⁷ The latter two reports were exclusively paediatric studies. A well validated prospective cohort study by Wood *et al* revealed a sensitivity of 88.9% and a negative predictive value as high as 99.5% for an elevation in WBC count.³ We tried to look at two interesting practical issues,

namely the timing of WBC count and the absolute cut-off levels to identify high risk. Most studies assessed WBC counts within 72 h of onset of symptoms, although counts up to 5 days were included by some. The definition of a significant cut-off WBC count varies among different authors, but most studies have quantified the risk to be very high above a WBC level of $11 \times 10^9/l$ – $13 \times 10^9/l$.²⁻⁵⁻⁷⁻⁹ None of the published studies suggest that leukocytosis is not a predictor for HUS.²⁻¹¹ Indeed, there is biological evidence to implicate the role of leukocytes in the pathogenesis of HUS.¹⁵

Leukocytosis has thus been unequivocally delineated as a reliable predictor for the development of HUS following *E coli* O157:H7 infection. Combining this with other putative risk factors, such as elevated C-reactive protein and albuminuria, might improve the accuracy of defining at-risk groups. Well children seen in the community or hospitalised children who recover rapidly may not require follow-up or investigations. However, where the diarrhoea has not resolved, a clinical impression of "well being" in the child has been shown to be unreliable as a reassuring factor.⁴⁻⁷ In such situations the use of validated risk factors is necessary to improve prognostic accuracy. Most of these children would have already had a full blood count and hence additional tests may not be required. A normal leukocyte count will provide reliable reassurance against progression to HUS in nine out of 10 cases.³ Similarly, leukocytosis will successfully predict progression to HUS in 70-90% of children.³⁻⁹

Interventions like early intravenous fluid therapy have already been proven to reduce the risk for progression to HUS, while other potential measures such as the use of toxin binders remain understudied.¹⁶ Formulation of a well defined risk assessment tool based on leukocytosis and other risk factors could help to identify high risk children and streamline the monitoring process and early use of appropriate interventions.

CLINICAL BOTTOM LINE

- Leukocytosis is a valid, independent and reliable early risk factor for predicting progression to HUS in children with *E coli* O157:H7 infection. (Grade B)
- The absence of an elevated WBC count during early stages of the illness makes HUS an unlikely event following *E coli* O157:H7 infection in children. (Grade B)
- Formulation of a well validated clinical decision rule (CDR) incorporating leukocytosis with other risk factors is likely to help with early identification of children at risk of developing HUS following *E coli* O157:H7 infection.

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Is a once daily dose of gentamicin safe and effective in the treatment of UTI in infants and children?

Report by
M Shahid, Department of Paediatrics, Portiuncula Hospital, Ballinasloe, County Galway, Ireland; muhdshahid@hotmail.com
R Cooke, Department of Paediatrics, Portiuncula Hospital, Ballinasloe, County Galway, Ireland
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An 8-month-old infant is admitted with fever and vomiting. Urinary tract infection (UTI) is diagnosed. You decide to commence IV treatment with gentamicin. In your paediatric ward, gentamicin is routinely administered in three times daily dose (TD) regimens but you look up gentamicin administration in the *BNF for children* and find that it can be given once daily (OD). This prompts debate amongst staff as to whether the same can be done on your ward. Everyone wonders whether there is any supportive evidence for efficacy and safety when OD gentamicin is used in the treatment of UTI.

Structured clinical question

In children aged 1 month to 18 years with UTI [patients], is OD gentamicin [intervention] as compared with TD gentamicin [comparator] as effective in resolving UTI and as safe [outcome]?

Search strategy and outcome

Secondary sources

Cochrane database, DARE, ACP Journal Club and EBM were explored. We could not find any systematic reviews explicitly answering our question.

Primary sources

Medline (Ovid Medline) 1966–February 2007

“Urinary Tract Infection” and “Gentamicin or gentam\$”

Table 3 Use of OD gentamicin in children with UTI

Citation	Study group	Study type (level of evidence)	Outcomes	Key results	Comments (key weaknesses)
Chong <i>et al</i> (2003) ¹¹	210 children (1 month to 9 years) recruited with presumed UTI. 172 were analysable (OD 84, TD 88). Mean age 11 months	Randomised controlled trial (RCT). OD dose at 5 mg/kg/day and TD dose at 6 mg/kg/day (level 1b).	Primary: Microbiological efficacy Secondary: Nephrotoxicity and ototoxicity	Microbiological efficacy OD vs TD (98.7% vs 97.7%, p=0.353) Nephrotoxicity (1.2% vs 2.3%, p=0.627) Ototoxicity (0 vs 0, p=0.506)	No mention how randomisation was done. 1-week follow up for assessment of adverse effects of ototoxicity and nephrotoxicity is questionable.
Carapetis <i>et al</i> (2001) ¹²	184 children (1 month to 12 years) with UTI were recruited. 179 were analysable (OD 90, TD 89)	RCT. Daily doses of gentamicin in both groups were 7.5 mg/kg/day (<5 years old), 6.0 mg/kg/day (5–10 years old) and 4.5 mg/kg/day (>10 years old) (level 1b).	Primary: Clinical efficacy (ie, cure) Secondary: Bacteriological efficacy, nephrotoxicity, ototoxicity	Clinical efficacy (cure): OD 96%, TD 98%. Relative risk (RR) of cure with OD gentamicin was 0.98 (95% CI, 0.93 to 1.03). Median (IQR) time to fever resolution in OD was 27 h (13.5 to 47.5), and in TD was 31.0 h (9.8 to 48) with p=0.61.	Follow-up for assessment of adverse events was incomplete. Author questions the sensitivity of the method used to detect nephrotoxicity.
Tapaneya-Olarn <i>et al</i> (1999) ¹³	49 children (6 months to 12 years) with presumed UTI enrolled in the study. 24 were analysable (OD 13, TD 11).	RCT. Gentamicin dose used was 4.5 mg/kg either OD or TD (level 2b).	Clinical and microbiological efficacy. Nephrotoxicity	Clinical efficacy (indicated by resolution of fever). Most patients in group afebrile by 24 h (mean 8.69 h) as compared with TD group (mean 15.31 h), p=0.067. Laboratory nephrotoxicity measured by urine N-acetyl-D-glucosaminidase (NAG)/creatinine ratio, was detected in 2/13 (15%) of patients in OD group and 5/11 (45%) in TD group with p=0.182.	Small sample size is the major weakness of this study. Also ototoxicity was not accounted as an adverse event.