cases where there was unanimity among our sample.[5,6] If such a change is to occur, however, we need a better understanding of the reasons why different surgeons take such divergent views and whether their perceptions coincide with those of patients and general practitioners. These topics are the subjects of a follow up study.

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Increased risk of diarrhoea caused by *Clostridium difficile* in elderly patients receiving cefotaxime

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Clostridium difficile is a Gram positive anaerobic spore forming bacillus whose pathogenicity is related to exotoxin production in the large bowel. This may result in disease ranging from trivial diarrhoea to life threatening pseudomembranous colitis. Between 1982 and 1993 there was a 15-fold national increase in reported *C difficile* infections that was most marked in patients aged over 65.[1] *C difficile* diarrhoea is almost exclusively acquired in hospital and strongly associated with the use of broad spectrum antibiotics.[1] In 1993 the British Thoracic Society recommended cefotaxime and cefuroxime as first line antibiotics for treating severe community acquired pneumonia of unknown cause in adults.[2] As a result the use of cefotaxime increased 20-fold in our unit. After November 1993 we also saw an unexpected increase in the incidence of *C difficile* diarrhoea, and we therefore sought to determine whether the two events were related.

Subjects, methods, and results

The geriatric unit at Hammersmith Hospital has 46 beds. We reviewed the clinical notes of all our patients with *C difficile* diarrhoea from April 1993 to November 1994. *C difficile* diarrhoea was defined as the passing of unformed stools in which *C difficile* toxin A was detected using a commercial enzyme immunoassay (Meridian Diagnostics Inc). In the case of a relapse only the first episode was counted. Affected patients were isolated or nursed together in a bay of the ward. "Notional courses" were used to estimate the total number of courses of each antibiotic (a seven day course of the most commonly prescribed dose regimen).[3]

From 1 April 1993 to 30 November 1994 1037 patients aged over 65 (median 83·8 years) were admitted; 43 (15 men) developed *C difficile* diarrhoea after antibiotic treatment. The average length of stay for these patients was 62 days, compared with 21 days for the whole group. Relapse of *C difficile* diarrhoea occurred in 11 of the 43 patients, and 18 (42%) died during their hospital admission; overall mortality in the unit was 25%. Two of the 43 patients were readmitted; data from the second admission were excluded from the results.

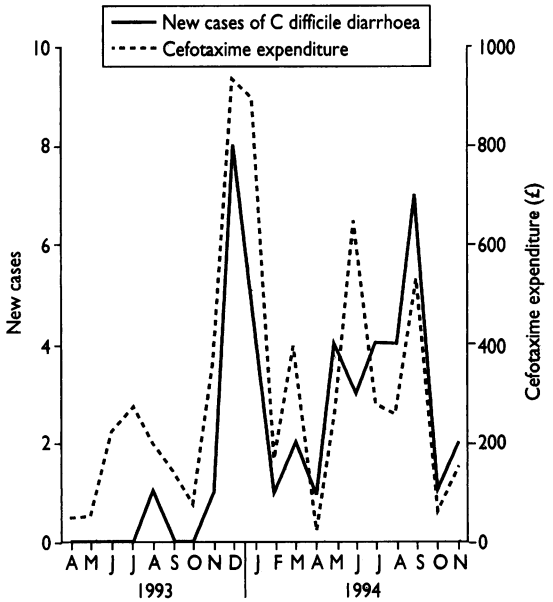
The monthly incidence of new cases of *C difficile* diarrhoea seemed to be strongly related to monthly expenditure on cefotaxime (figure). Expenditure on other antibiotics did not have such clear temporal relation. Moreover, the highest relative risk for developing diarrhoea among patients receiving an antibiotic compared with those not receiving it occurred with cefotaxime (7·2, 95% confidence interval 3·9 to 13·2), followed by cefuroxime (5·2 (2·9 to 9·45)), and erythromycin (2·8 (1·5 to 5·2)). No significant increased risk occurred with other antibiotics. Although many patients received combination therapy the data were not available to study the potential interaction between different agents.

Comment

A sudden increase in the incidence of *C difficile* diarrhoea followed a 20-fold increase in the use of cefotaxime. Infection control measures did not succeed in preventing new cases, which only decreased when the use of cefotaxime was stopped (figure). Nearly one in five patients who received cefotaxime developed *C difficile* diarrhoea.

Risk factors for the development of *C difficile* diarrhoea include increasing age; hospitalisation; malignancy; renal impairment; use of antibiotics, nasogastric feeding, laxatives, H_2 antagonists; and general disability. Many of these existed in our patients, but we could not firmly assess their risk ratios in our retrospective analysis.

C difficile diarrhoea has been reported following the administration of cefotaxime,[4] but we are not aware of any report of such a rapid increase in cases related to its introduction. Another recent study did, however, show a similar relation with another broad spectrum antibiotic, clindamycin.[5] We suggest cefotaxime should be used in elderly patients only if there is no suitable alternative.



Relation between use of cefotaxime (as measured by expenditure) and new cases of C difficile diarrhoea, April 1993 to November 1994

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Prospective seroepidemiological evidence that human papillomavirus type 16 infection is a risk factor for oesophageal squamous cell carcinoma

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The genome of the major type of human papillomavirus that is associated with anogenital cancer, HPV16, is occasionally found in non-genital cancers, such as oesophageal cancer and various cancers of the head and neck,[1] but it is not clear whether human papillomavirus infection is a measurable risk factor for these cancers. Since seropositivity for HPV16 capsids has documented specificity for HPV16 infection,[2] serological testing can provide information on whether HPV16 infection is a risk factor for disease development. Previously we found that HPV16 capsid seropositivity was a risk factor for both cervical and anal cancers at odds ratios of 9·5 and 30·4 respectively.[3] Therefore we designed a prospective study to assess whether HPV16 infection is also a risk factor for oesophageal or head and neck cancers.

Subjects, methods, and results

During 1968-72 the mobile clinic of the Social Insurance Institution of Finland collected serum samples from 39 268 subjects resident in most parts of Finland.[4] Registry linkage with the nationwide Finnish Cancer Registry identified 165 cases of head and neck cancers that had occurred in the cohort up to 1991. For each patient with cancer, two controls (free of any cancer at baseline) were selected, matched for sex, age, and municipality. In 134/165 matched sets the ages were exactly matched. The maximum age discrepancy (in 4/165 sets) was seven years. The matching for municipality also resulted in a matching for time of sample collection. Detection of IgG against HPV16 capsids was performed by standard enzyme linked immunosorbent assay (ELISA).[3] Relative risks, estimated as odds ratios, were calculated using conditional logistic regression of non-dissociable matched sets.

At a preassigned cut off level (0·180 absorbence units; relative to internal standards the same as previously used[3]) 39/492 serum samples were positive to HPV16 capsids. The proportions seropositive were similar in the subjects who acquired head and neck cancer and the controls. However, 7/29 subjects who acquired squamous cell carcinoma of the oesophagus and 8/39 subjects who developed any oesophageal cancer were HPV16 seropositive compared with only 2/78 matched controls ($P < 0·001$; table). Calculation of odds ratios for two alternative, arbitrarily assigned cut off levels (0·150 and 0·200) resulted in similar or identical odds ratios. HPV16 seropositivity was not significantly related to age, sex, time lag until diagnosis of disease, or smoking status.

Relative risk of developing head and neck cancers among HPV16 seropositive subjects

Primary site of cancer	No positive for HPV16/total No of cases	% Of positive cases	Odds ratio (95% confidence interval)	Smoking adjusted odds ratio (95% confidence interval)
Oesophagus	8/39	21	14·6 (1·8 to 117)	13·1 (1·6 to 108)
Larynx	1/37	3	0·2 (0·0 to 1·6)	0·2 (0·0 to 2·0)
Lip, tongue, salivary	4/60	7	0·7 (0·2 to 2·2)	0·6 (0·2 to 2·1)
Other oral	1/29	3	0·6 (0·1 to 7·4)	0·4 (0·0 to 7·1)

Comment

The major risk factors for oesophageal cancer (smoking, alcohol consumption, low socioeconomic status, nutritional deficiencies, certain chemical agents) have not fully explained the geographical variation of the disease.[1] In some cultural settings smoking and drinking habits and socioeconomic status are associated with sexual behaviour and thus also with HPV16 infection.[5]

The risk associated with HPV16 is, however, unlikely to be a secondary association since (*a*) adjustment for smoking habits did not affect the HPV16 related risk (table), (*b*) the risk of cancer associated with HPV16 was considerably higher than the risk associated with these other risk factors, and (*c*) as assessed in a comparable Swedish cohort, HPV16 seropositivity was only weakly associated with alcohol consumption (maximum odds ratio at any exposure level: 2·0 (1·1 to 3·8)) and, as in this cohort, not associated with smoking regardless of exposure level (J D and I Kallings, unpublished). Epidemiological studies of possible interactions between HPV16 seropositivity and other risk factors might be important in elucidating the cause of oesophageal cancer.

Whereas cervical human papillomavirus infection is a sexually transmitted disease,[5] the mode whereby the virus infects the oesophagus is unclear. Human papillomavirus of types 6 and 11 can be transmitted at birth and cause juvenile respiratory papillomatosis, whereas oral condyloma in adults can be contracted by oral/genital sex. Future studies will need to clarify the frequency and duration of oesophageal human papillomavirus infection as well as the mode of transmission. It will also be interesting to determine to what extent exposure to human papillomavirus differs between populations at high or low risk for oesophageal cancer.

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