Antibiotic policies and Clostridium difficile-associated diarrhoea

SIR—We were interested to read the paper by Ludlam et al. on the cost-effectiveness of an antibiotic policy to reduce the risk of Clostridium difficile-associated diarrhoea [1]. In the elderly care unit at Southampton General Hospital we have similarly shown the efficacy of reducing the incidence of C. difficile-associated diarrhoea by altering the antibiotic policy, but we have adopted a cheaper strategy.

An audit of patients with C. difficile-positive stool results on our unit between 1 February 1998 and 14 March 1998 revealed a 30% incidence of C. difficile-associated diarrhoea for those patients treated with intravenous ceftaxime or cefuroxime. During the same period, no cases were found among patients who received intravenous ampicillin or co-amoxiclav. Most of these patients had community-acquired pneumonia and were being treated in line with the British Thoracic Society guidelines. Elderly patients usually fall into the ‘severe’ category of these guidelines, for which second- or third-generation cephalosporins are recommended.

We amended the guidelines for these elderly patients, recommending intravenous benzylpenicillin, trimethoprim and a single dose of gentamicin. This policy was implemented in May 1999 on the elderly care wards, but not on the general medical wards. The absolute number of cases of C. difficile diarrhoea on our wards fell from 38 in the first quarter of 1999 to 14 in the third quarter, while the corresponding numbers of cases on the medical wards were 31 and 33.

Following implementation of this policy, use of second- and third-generation cephalosporins has been reduced by 62% in the elderly care unit, with no attributable increase in injectable antibiotic costs. Furthermore, our antibiotic choice has additional advantages over the ciprofloxacin and benzylpenicillin combination chosen by Ludlam et al. Nearly 60% of Staphylococcus aureus bacteraemia in our unit is due to multi-resistant S. aureus (MRSA), and previous empirical treatment for sepsis of unknown origin with cephalosporins was unlikely to be effective against MRSA. Currently, over 60% of MRSA isolates are sensitive to trimethoprim and over 90% sensitive to gentamicin. Neither ciprofloxacin nor benzylpenicillin are active against MRSA. The change in antibiotic policy has had no impact on other antibiotic sensitivity data from our unit. Coliform sensitivity to trimethoprim, which is largely determined by trimethoprim use in general practice, has remained at 75%, while coliform sensitivity to gentamicin has remained at 99%.

Our antibiotic policy is far cheaper than that employed by Ludlam et al. (who used intravenous ciprofloxacin), and we would recommend it as a cost-effective policy.

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Measuring disability and mortality following relocation within the National Health Service

SIR—The closure of any NHS continuing care unit is controversial, particularly in cases when patients are moved elsewhere. Terms such as relocation stress, transplantation shock, transfer trauma and pure relocation effect have been used to describe the physical and psychological effects on older individuals who are moved. Although there is much written about transfer, results are often contradictory and ambiguous. The UK, despite the large number of NHS ward closures, has produced few prospective patient follow-up studies.

In 1997, our local health authority decided to close two NHS long-term continuing care wards. The concern to avoid the situation which occurred in the Napsbury to Elmstead transfer [1] (where seven patients died within 3 weeks of moving), the enormous local media attention and families’ concern over the health of their relatives, prompted an investigation to examine the disability and mortality following relocation. The outcome in patients who were relocated—designated either frail elderly (FE) or elderly mentally infirm (EMI)—was compared with that in age- and sex-matched patients who remained in the hospital. Twenty relocated patients (seven FE and 13 EMI) and 42 who were not relocated (17 FE and 25 EMI) were assessed just before relocation and 3, 6, 9 and 12 months post-transfer. Disability was measured using the Barthel index and any change following the move compared using the Mann–Whitney U test. Differences in mortality between groups were compared using the χ² test.

There was no difference in age between the groups (mean age range = 78.2–83.7) but the EMI patients who were moved had statistically significant lower baseline Barthel scores than the EMI patients who were not moved (median = 1 vs 7, P = 0.0021). There was no
difference between pre-move Barthel score and either first recorded or the final recorded post-move score. One-year mortality ranged from 20% in the EMI control group to 29% in the FE patient group but these differences were not significant. When patients with baseline Barthel scores of $>5$ were excluded from the analysis, again no significant difference in Barthel and mortality was found.

In this study, moving older people was not associated with an increase in mortality or disability following relocation. This contrasts with the results of a number of other studies which we have reviewed in detail elsewhere [2]. However, we took particular care in the planning and organization of the move, and we hope that this had a beneficial influence on post-relocation measures. More UK investigations are needed into the effects of transferring vulnerable older individuals.

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**Spontaneous rupture of oesophagus (Boerhaave’s syndrome) related to rivastigmine**

SIR—Alzheimer’s disease is a progressive degenerative disorder characterized by deficits in deficits and memory and cognition that are associated with loss of presynaptic cholinergic function in the brain. Cholinomimetics might improve cognitive performances in patients with Alzheimer’s disease. The efficacy of various acetylcholinesterase (AChE) inhibitors including tacrine, donepezil and rivastigmine has been confirmed in clinical trials, but the safety profile of these drugs is still uncertain [1]. We describe the onset of the potentially fatal spontaneous rupture of the oesophagus (Boerhaave’s syndrome) associated with untitrated use of rivastigmine tablets in a patient with Alzheimer’s disease.

A 67-year-old, married, caucasian woman presented with a 2-year history of progressive memory loss. Other than arterial hypertension (successfully managed with lisinopril 10 mg/day) her medical history was unremarkable, with no history of ethanol abuse. On initial evaluation, she had impaired memory and orientation—Mini-Mental State Examination (MMSE) score 23/30. As there were no relevant findings on neurological and general examination, a diagnosis of probable Alzheimer’s disease according to NINCDS-ADRND criteria [2] was made.

Rivastigmine was initiated at a dose of 1.5 mg/day and was increased in weekly increments of 1.5 mg up to 9 mg/day. No adverse events were reported during the titration period of 6 weeks. After 13 weeks of therapy (including titration phase), weight loss was observed. Rivastigmine was discontinued and no other medication was prescribed. Eight weeks later, marked cognitive deterioration was seen (MMSE score 19/30) and the patient and her carer were advised (orally and in writing) to re-start 1.5 mg/day rivastigmine. However, she mistakenly took one tablet of 4.5 mg of rivastigmine in the afternoon, instead of following her previous dosage regimen.

About 30 min later she started to vomit several times. Nearly 2 h later she complained of severe chest pain, followed by high-grade fever. A chest X-ray showed mediastinal and soft tissue emphysema. A water-soluble contrast X-ray examination (Gastrografin) showed rupture of the distal part of oesophagus. An emergency surgery procedure with primary repair and drainage was performed. She recovered without complications and 6 weeks after surgery, was discharged home in relatively good condition.

Spontaneous rupture of oesophagus is an uncommon, but life-threatening clinical condition. It has varying modes of presentation, making the diagnosis a difficult clinical challenge. Emergency surgery within 12 h of onset is usually life-saving. Most patients are chronic alcohol abusers, but the syndrome is rarely associated with drug intake [3]. Rivastigmine and others AChE inhibitors may produce gastrointestinal adverse reactions (nausea, vomiting, abdominal cramps), but the frequency and severity of gastrointestinal adverse reactions might be reduced with careful titration of rivastigmine at the beginning of treatment [4, 5]. It is well known that AChE inhibitors may produce chest pain because of increased oesophageal contractions [6], although the consequent spontaneous rupture of oesophagus has not been reported previously.

In this case, we believe that the occurrence of severe vomiting with consecutive onset of spontaneous rupture of oesophagus may be a consequence of the lack of titration of rivastigmine. This confirms the necessity of careful titration of rivastigmine, even when re-starting treatment.

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Optimizing management of congestive heart failure in older people

SIR—Congestive heart failure (CHF) is primarily a disorder of older people, the incidence rising exponentially with advancing age. Recent advances in pharmacological management have demonstrated how morbidity, mortality and associated hospitalizations could be reduced with the appropriate use of angiotensin-converting enzyme (ACE) inhibitors, and add-on and alternative medical therapies [1–3]. Despite accumulating evidence for the efficacy of such treatments, the management of CHF is often haphazard and not targeted to patient need, especially in older people. The outcome of suboptimal management is not only increased morbidity and mortality but also repeated hospital readmission which, for older people, is associated with increased dependency and institutionalization.

Non-pharmacological strategies to improve CHF management and reduce risk of hospital readmission have centred on nurse-led community intervention programmes. Recent clinical trial evidence supports the effectiveness of a nurse-led home-based intervention for older CHF patients, with an associated reduction in healthcare costs [4]. However, it is unlikely that such specialist services can be developed by all departments of geriatric medicine. An alternative strategy may be to involve CHF patients and their principal carers in the organization and delivery of care through the provision of evidence-based self-monitoring and management algorithms. Such a strategy should empower the patient/carer to direct their care according to best practice.

The University Department of Geriatric Medicine in Sunderland hosts an age-related, unselected, emergency medical admissions service for all patients aged 70 years and over. There are 5500 emergency admissions to the department per annum, 20% of which are readmissions within 12 weeks of most recent discharge. The most frequently readmitted diagnostic group is patients with CHF, representing 21% of all readmissions. A previous study of CHF patients readmitted to our department within 12 weeks of discharge identified suboptimal prescribing of ACE inhibitors, with a reluctance both to initiate and subsequently to titrate to the maximum tolerated ACE inhibitor dose [5]. Furthermore, poor patient knowledge and compliance with treatment after discharge was highly prevalent.

As part of a study to determine whether the provision of patient/carer self-management algorithms for CHF is effective in improving outcomes for older patients discharged from hospital, we sought to implement best practice for the inpatient management of CHF through the establishment of an evidence-based clinical protocol. The protocol was developed by a multidisciplinary group (consultant geriatrician, specialist nurse, pharmacist, and general practitioner). User awareness of the protocol was promoted in a series of meetings with all doctors, senior nurses and pharmacists involved in care of CHF patients within the department.

To determine the impact of the protocol on clinical practice, we examined the management of CHF before and after its introduction by comparing 50 consecutive patients admitted with CHF during the 3 months before protocol implementation with 50 consecutive CHF patients admitted in the 3 months after implementation. Patient groups were equally matched for age, sex and severity of CHF (New York Heart Association classification). Principal results are presented in Figure 1. Referral for echocardiogram, prescription of ACE inhibitors whilst in hospital and use of intravenous diuretics in accordance with recommended practice were all significantly increased (\(P = 0.041\), \(P = 0.082\) and \(P = 0.016\) respectively). Titration to the maximum tolerated dose of ACE inhibitor was not significantly altered, despite advice

Figure 1. The impact of the protocol on heart failure management in before (■) and after (○) the introduction of the protocol. ACEI, angiotensin-converting enzyme inhibitor. (\(n = 50\) in each group).
in the protocol which had been agreed and accepted by all admitting geriatricians.

CHF is a progressive condition and there is evidence that patients with this condition benefit from frequent monitoring and dose adjustments after discharge from hospital. We have demonstrated how simple inpatient clinical protocols can improve CHF management. The continuing reluctance of clinicians to initiate ACE inhibitors and titrate doses to the maximum tolerated illustrates the importance of further patient follow-up in CHF care.

We are now undertaking a randomized controlled trial using disease self-management algorithms to provide older patients (and their carers) with the necessary knowledge, skills and advice to assume responsibility for their own CHF management following hospital discharge. It remains to be determined whether such a strategy will maximize treatment options or be associated with improved clinical outcomes.

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Major aphthous ulcers induced by nicorandil

SIR—We report a case of severe aphthous mouth ulceration after use of nicorandil.

Nicorandil (Ikorel, Rhône–Poulenc Rorer Ltd) is a potassium channel activator used in the treatment of angina pectoris [1]. An established mucos-cutaneous side effect of nicorandil is cutaneous erythema [2] but the drug has recently been implicated in recurrent aphthous stomatitis and ulcers.

A 68-year-old woman with a history of ischaemic heart disease was admitted with central chest pain. Acute myocardial infarction was excluded and she was treated for unstable angina with low-molecular-weight heparin and nitrate infusions. Along with other antianginal medications (atenolol, diltiazem, nitrates, aspirin), she was already receiving nicorandil 10 mg twice daily on admission. The dose of nicorandil was increased to 20 mg twice daily. None of her other medications was altered. Within a week, her angina settled and she was discharged.

One week later, she developed large (2–3 cm diameter), painful aphthous ulcerations on the tongue, inside of cheeks and gingiva (Figure 1). There were no extra-oral signs. She did not complain of any other side effect of nicorandil and was otherwise well. Laboratory investigations showed no abnormalities in white blood cells or haemoglobin, or in kidney and liver function tests. No other local, systemic or other cause of mouth ulcers could be detected.

Treatment with topical steroids and symptomatic treatment failed to induce ulcer healing. Withdrawal of nicorandil was followed by resolution of the oral lesions within 4 weeks. Her other medications were continued as before. She has remained well at her follow-up 3 months later.

In this case, the role of nicorandil in the causation of mouth ulcers is highly probable as the ulcers occurred after a change in the dose. Moreover, her other drugs are not known to be associated with oral ulcers. We could identify no other causative factor. The oral lesions healed spontaneously after the withdrawal of nicorandil.

Nicorandil is a widely prescribed and well tolerated antianginal drug. It has been available in Japan for more than 10 years and severe mouth ulceration as a side effect has not been reported there. It has been licensed and available in Europe and UK since 1994. In France, several cases of mouth ulcers attributed to nicorandil have been reported to the Centre de Pharmacovigilance [3–9]. There has been only one published report

Figure 1. Nicorandil-associated ulcerations on the tongue.
of three cases of nicorandil-induced oral ulcers in the UK [10].

Table 1 summarizes details of reported cases of nicorandil-induced oral ulceration. Most reported cases have involved the tongue. The ulcers present within 3 months of starting nicorandil and complete healing occurs after drug withdrawal. As yet, there is no mention of oral ulceration in the British National Formulary as an adverse effect of nicorandil.

The mechanism for nicorandil-induced ulceration remains unclear. Metabolites of nicorandil could concentrate in the saliva, especially in elderly patients. A past history of aphthae could be a cofactor of this side effect [4]. Our patient gave no history of oral ulcers. It has been suggested that a minimum dose of nicorandil of 30 mg per day is necessary to induce mouth ulcers [6]. Our patient developed the side effect when the dose was increased from 20 to 40 mg per day. In the largest reported series of 16 patients (age range 64–90 years), 12 were on a dose of 40 mg/day and four on 60 mg/day, and aphthous ulceration after dose increase was seen in two patients, suggesting a dose-dependent mechanism [7]. In all published series, complete healing occurred after discontinuation of the drug. However, on experimentally induced gastric ulcers in rats, nicorandil administered orally produced an anti-ulcer effect through its potassium (ATP) channel-opening property [11].

Clinicians should be aware that nicorandil can be a potential inducer of multiple and sometimes giant aphthous ulcerations.

Table 1. Summary of reported cases of nicorandil-associated oral ulceration

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of cases</th>
<th>Country</th>
<th>Time from start of nicorandil</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boulinguez et al., 1997 [3]</td>
<td>3</td>
<td>France</td>
<td>2–4 months</td>
<td>Tongue, gingival, labial mucosa</td>
</tr>
<tr>
<td>Riechert et al., 1997 [4]</td>
<td>2</td>
<td>France</td>
<td>15 days after dose increased to 3 weeks</td>
<td>Tongue, hard palate, labial and buccal mucosa</td>
</tr>
<tr>
<td>Cribier et al., 1998 [5]</td>
<td>7</td>
<td>France</td>
<td>Immediate to 30 months</td>
<td>Tongue, buccal, gingival mucosa</td>
</tr>
<tr>
<td>Desruelles et al., 1998 [6]</td>
<td>2</td>
<td>France</td>
<td>1–2 months</td>
<td>Tongue, oral mucosa</td>
</tr>
<tr>
<td>Agbo-Godeau et al., 1998 [7]</td>
<td>16</td>
<td>France</td>
<td>2–36 months</td>
<td>Tongue, gingiva, cheeks</td>
</tr>
<tr>
<td>Roussel et al., 1998 [8]</td>
<td>5</td>
<td>UK</td>
<td>1–3 months</td>
<td>Tongue and fauces</td>
</tr>
</tbody>
</table>

We thank David Hughes and Leighton Evans for providing us with the necessary information about nicorandil.

Centenarians at no cost of reproductive success

SIR—An unprecedented number of individuals around the world are reaching their centennial in the absence of overt or severe diseases. Nevertheless, the evolutionary theories of ageing [1] and experiments in non-human species [2] indicate that longevity requires somatic investments that reduce the resources available for reproduction. Furthermore, a study of the British aristocracy supports an evolutionary trade-off between longevity and reproduction, showing that women who lived longer had fewer children [3].

Using town censuses, we located and recruited 88 centenarian women (median age 101 years, range 100–108), and collected data on their progeny. All women...
were married and live (or have lived) in Calabria (Southern Italy) during the twentieth century. Only four of them were childless, and for those women who had children, the median number was 5 (range 1–12). Evolutionary theories of ageing [1], predictions in humans of experiments in *Drosophila melanogaster* [2] and Westerdorp and Kirkwood’s conclusions [3] are not supported by our findings. Calabrian centenarian women and their progeny are a good example of successful ageing with no reproductive cost.

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