Saturday 8 June 2002

BMJ

Managing antibiotic associated diarrhoea

Probiotics may help in prevention

Papers p 1361

Diarrhoea is a common adverse effect of antibiotic treatments. Antibiotic associated diarrhoea occurs in about 5-30% of patients either early during antibiotic therapy or up to two months after the end of the treatment.[1–3] The frequency of antibiotic associated diarrhoea depends on the definition of diarrhoea, the inciting antimicrobial agents, and host factors.

Almost all antibiotics, particularly those that act on anaerobes, can cause diarrhoea, but the risk is higher with aminopenicillins, a combination of aminopenicillins and clavulanate, cephalosporins, and clindamycin.[1 4 5] Host factors for antibiotic associated diarrhoea include age over 65, immunosuppression, being in an intensive care unit, and prolonged hospitalisation.[6]

Clinical presentations of antibiotic associated diarrhoea range from mild diarrhoea to fulminant pseudomembranous colitis. The latter is characterised by a watery diarrhoea, fever (in 80% of cases), leucocytosis (80%), and the presence of pseudomembranes on endoscopic examination. Severe complications include toxic megacolon, perforation, and shock.

Antibiotic associated diarrhoea results from disruption of the normal microflora of the gut by antibiotics. This microflora, composed of 10^{11} bacteria per gram of intestinal content, forms a stable ecosystem that permits the elimination of exogenous organisms. Antibiotics disturb the composition and the function of this flora and enable overgrowth of microorganisms that induce diarrhoea. Since demonstration of its role in 1978, *Clostridium difficile* has emerged as the major enteropathogen of antibiotic associated diarrhoea.[3] This anaerobic spore forming bacteria is responsible for 10-25% of cases of antibiotic associated diarrhoea and for virtually all cases of pseudomembranous colitis.[3] It works by secreting two potent toxins that cause mucosal damage and inflammation of the colon. Other infectious agents reported to be responsible for antibiotic associated diarrhoea include *C perfringens*, *Staphylococcus aureus*, *Candida* spp, *Klebsiella oxytoca*, and *Salmonella* spp.[7] However, their role in the pathogenesis of diarrhoea is still debated because most of them are considered to be usual commensal bacteria of the gut flora. Antibiotic associated diarrhoea can also result from a decrease in metabolism of carbohydrates and bile acids.[7]

Managing the diarrhoea depends on the clinical presentation and the inciting agent.[7–10] In mild to moderate diarrhoea conventional measures include rehydration or discontinuation of the inciting agent or its replacement by an antibiotic with a lower risk of inducing diarrhoea, such as quinolones, co-trimoxazole, or aminoglycosides. In 22% of cases of diarrhoea related to *C difficile*, withdrawal of the inciting agent will lead to resolution of clinical signs in three days.[11]

In cases of severe or persistent antibiotic associated diarrhoea, the challenge is to identify *C difficile* associated infections since this is the most common identifiable and treatable pathogen. Diagnosis relies on detecting toxins A or B in stools. Tissue culture assay is the gold standard, although it is time consuming. Enzyme immunoassays for toxins A or B have a good specificity but a false negative rate of 10-20%.

Treatment of *C difficile* related diarrhoea is based on oral metronidazole (250 mg four times daily) or oral vancomycin (125 mg four times daily) for 10 days.[11 12] The response to metronidazole or vancomycin is similar (>90%), and diarrhoea usually resolves in two or three days. The Infectious Diseases Society of America, the American College of Gastroenterology, and the Society for Hospital Epidemiology of America recommend metronidazole as the first line of treatment to prevent the emergence of vancomycin resistant organisms.[9 10] Vancomycin should be reserved for those with severe illness, intolerance to metronidazole, failure to respond to metronidazole, or pregnancy. Antiperistaltic agents should be avoided because of the risk of retention of toxins in the lumen. About 20% of patients with *C difficile* related diarrhoea will relapse. Most patients will respond to another course of metronidazole or vancomycin, but 5% will experience several relapses; the management of these remains controversial.

As antibiotic associated diarrhoea mostly results from a disequilibrium of the normal intestinal flora, research has focused on the benefits of administering living organisms (probiotics or biotherapeutic agents) to restore the normal flora. Numerous probiotics such as *Lactobacillus acidophilus*, *L casei* GG, *L bulgaricus*, *Bifidobacterium bifidum*, *B longum*, *Enterococcus faecium*, *Streptococcus thermophilus*, or *Saccharomyces boulardii* have been tested for the treatment and prevention of antibiotic associated diarrhoea.[13] The benefits of probiotics are unproved as few have been evaluated in double blind placebo controlled studies. The results of the small and open trials of treatment are conflicting.

Most studies with probiotics have assessed their use in preventing antibiotic associated diarrhoea. In this issue D'Souza et al report a meta-analysis of nine randomised double blind trials comparing probiotics with

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placebo in the prevention of diarrhoea (p 1361).[14] Among these studies, four trials were used *S boulardii* and five *Lactobacillus*. Their results suggest that probiotics are useful in prevention. The expected advantages of probiotics include ease of administration, cost effectiveness, and relative lack of side effects. However, several cases of bacteraemia with *S boulardii* have been reported, which should prompt caution in the use of this yeast in immunosuppressed patients or patients with underlying disorders.

The key measure for preventing antibiotic associated diarrhoea, however, is to limit antibiotic use. Probiotics have proved useful in preventing diarrhoea, but the number of clinical trials is limited and further controlled trials using different probiotics are needed. In the case of *C difficile* related diarrhoea hygiene measures (single rooms, use of gloves, and handwashing) should be systematically associated with treatment in order to prevent transmission and dissemination of this nosocomial bacteria.

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The power of the press in smokers' attempts to quit

Doctors propose, the press disposes

In April 2002, the National Institute for Clinical Excellence (NICE) released guidance on cost effective pharmacological treatment of tobacco addiction.[1] This endorsement allows every health authority in England and Wales to provide nicotine replacement or bupropion for patients who are dependent on tobacco and request treatment. Whether smokers will ask for and receive these drugs depends on many factors. Two scenarios, from the United Kingdom and the United States, illustrate the struggle between the press and medical experts to investigate and report concerns about the safety of new drugs for smoking cessation and the effect this struggle has on reported attempts to quit smoking.

The NHS advanced the treatment of the tobacco dependence movement with three initiatives: a white paper that established a priority for the treatment of tobacco dependence in 1998,[2] a national plan for expanded smoking cessation services launched in 1999-2000, and the approval of bupropion in 2000 and nicotine replacement in 2001 for inclusion in the NHS reimbursement scheme. The Royal College of Physicians also published a report urging all doctors to treat nicotine addiction as a major medical and social problem.[3]

A new era dawned when the release of bupropion hydrochloride, which is a non-nicotine agent and is available by prescription only, required a doctor's direct involvement in patients' attempts to stop smoking. But most doctors were not trained and do not feel competent to treat tobacco dependent patients,[4] despite the information on bupropion they have received from the government and the pharmaceutical industry. The print and television media heralded bupropion as a wonder drug when it was released in 2000. Not surprisingly, after the announcement of reimbursement for bupropion by the NHS, smokers queued up in waiting rooms, expecting their tobacco addiction to vanish with this new pill.

The public enthusiasm changed abruptly in February 2001, when a London newspaper reporter published a series of articles that profiled a few dramatic reports of deaths in smokers using bupropion.[5] Other newspapers and BBC's *Healthcheck* programme picked up the stories, and soon all of Europe heard about these deaths. Predictably, the number of people receiving prescriptions for bupropion declined from 29% to 21.5% from April to September 2001.[6] The number of patients at the centres had increased every quarter from March 1999 to 68 000 in the first quarter of 2001. After this, the demand for treatment diminished and a third fewer smokers were treated six months later. If this rise and fall is simply due to new year's resolutions and a no smoking day on 13 March and not to the escalating negative media stories a similar decline should re-emerge in 2002.

The Medicines Control Agency officially maintains that the contribution of bupropion in the 58 deaths reported since June 2000 remains unproved, and

BMJ 2002;324:1346–7