Effectiveness bulletins

Antimicrobial prophylaxis in colorectal surgery

Anne-Marie Glenny, Fujian Song

This paper is based on *Effective Health Care*, volume 4, no 5, which is an update of a systematic review of randomised controlled trials (RCTs) examining the effectiveness of different antimicrobial regimens used for the prevention of surgical wound infection in patients undergoing colorectal surgery. Details of the review's methodology are published elsewhere.[1 2]

Hospital acquired infections, of which surgical wound infections are among the most common, cost the NHS over £170m in England alone.[3] These infections increase morbidity and mortality, prolong hospital stay, and increase the cost of medical care.[4 5]

Colorectal surgery is associated with a particularly high risk of surgical wound infection due to a high risk of contamination by bacteria from the contents of the large bowel. The use of antimicrobial prophylaxis can help to reduce the risk of wound infections after colorectal surgery from about 40%[6] to around 11%.[1 2]

Over the past 20 years, the practice of using antimicrobial prophylaxis before surgery has evolved greatly, with such antimicrobial agents accounting for about half of all antibiotics prescribed in hospitals.[7] Uncertainty exists, however, about which drugs should be used, and about the timing, duration, and route of administration.[8] In addition, thought needs to be given to ways of reducing the spread of antimicrobial resistance.[9]

NHS Centre for Reviews and Dissemination, University of York, UK
A-M Glenny
F Song

Correspondence to:
Ms A-M Glenny, NHS Centre For Reviews and Dissemination, University of York, YO10 5DD, UK.

Accepted 28 January 1999

Effectiveness of antimicrobial prophylaxis

ANTIBIOTICS *v* NO ANTIBIOTICS

As wound contamination by pathogenic bacteria is common and host resistance is often defective, antibiotic prophylaxis should play an important part in preventing infection after colorectal surgery. A systematic review published in 1981 concluded that "no-antibiotic" control groups should not be considered in further trials of colorectal surgery.[10] Since then, however, four RCTs which did use a no-antibiotic control group and met the inclusion criteria for the bulletin, have been published.[11–14] All showed a greatly reduced surgical wound infection rate in the antibiotic group (12.9% *v* 40.2%: pooled (odds ratio) OR = 0.24, 95% CI 0.13 to 0.43) (fig 1). This shows that antimicrobial prophylaxis for colorectal surgery is effective and should be used.

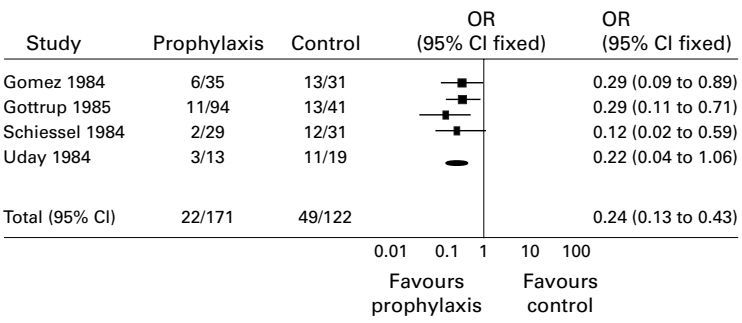

Figure 1 Antibiotic prophylaxis v no antibiotic control.

Choice of antimicrobial agent

A total of 152 RCTs were identified, examining more than 70 different antibiotic regimens. It was not possible, however, to identify an optimal antimicrobial prophylaxis regimen. The estimates of effectiveness were similar for many of the regimens studied, but it is uncertain that all these regimens are equally effective. The lack of statistically significant findings in over 80% of the included trials may be due, in part, to small sample sizes.

Inadequate regimens

Although an optimal regimen could not be identified, certain regimens were shown to be less effective for preventing surgical wound infection in colorectal surgery because of inadequate antimicrobial coverage, or inappropriate timing and dosage. For example, the administration of metronidazole alone was shown to be significantly less effective than metronidazole used in combination with ampicillin,[12] doxycycline,[15] cefuroxime,[16 17] netilmicin,[16] or fosfomycin.[18] This is because metronidazole is active against anaerobic bacteria but ineffective against aerobic bacteria. As both kinds of micro-organisms are present in the bowel, metronidazole should be combined with other antibiotics that are active against aerobic bacteria.

The following antibiotics used on their own were shown to be inadequate at preventing surgical wound infection: metronidazole,[12 15 17] neomycin,[19] gentamicin,[20] doxycycline,[21 22] cefotaxime,[23] tinidazole,[24–26] and piperacillin.[27 28]

First generation *v* new generation cephalosporins

A comparison between first generation cephalosporins and the new generation (second and third generation) cephalosporins was undertaken in six trials (reported in five articles).[29–33] No statistically significant differences between groups were shown in any of the trials. Similarly, pooling of the results from the six trials did not produce a statistically significant difference between the first generation and new generation cephalosporins (overall rate of surgical wound infection: 6.0% *v* 6.4%; OR = 0.93; 95% CI 0.46 to 1.86).

Timing and duration of administration

By definition, prophylactic use of antimicrobial agents means administration before the onset of infection. To prevent post-operative infection, it is crucial that the concentration of antibiotics in the tissue surrounding the surgical wound should be sufficient at the time of bacterial contamination.[6 34] The duration of the antibiotic regimen, however, is not so clear.

A total of 17 trials identified in the review compared a single dose regimen with a multiple dose regimen, using the same antibiotic or combination of antibiotics. None of these trials found a significant difference in post-operative surgical wound infection rate between the two regimens. Pooling of the results from the 17 trials again showed no significant difference between single and multiple dose regimens (10.6% *v* 9.7%; OR 1.17; CI 0.89 to 1.54)

No evidence exists to suggest that continuing to give antibiotics after the end of the operation reduces the risk of surgical wound infection. Extended use of antibiotics is wasteful and potentially hazardous.

The duration of the operation and the half life of an antibiotic may be related to the effectiveness of single dose or short term use of antibiotic prophylaxis. One study has reported that an extended duration of an operation is associated with a higher rate of surgical wound infection.[35] However, trials comparing single and multiple dose regimen and reporting duration of operation were unable to provide any convincing evidence about the relation between the efficacy of single dose regimen and the duration of operation.[36–38] Clinicians need to consider other factors associated with an increased incidence of infection, such as the need for blood transfusion,[36 39] to decide whether a second dose is required when surgical procedures last more than two hours.

Route of administration

Prophylactic antibiotics can be given via the gastrointestinal system, parenterally or topically.[40] Establishing the efficacy of different routes of administration of antimicrobial prophylaxis was complicated by the lack of studies addressing this specific question.

No additional benefit was observed in six trials that compared parenteral alone with parenteral plus topical use of antimicrobial prophylaxis.[41–46] One study compared parenteral administration with an intraoperative intraperitoneal plus subcutaneous application.[47] Both groups received the same antibiotic (cephazolin). No statistically significant difference was shown between the two groups with regard to surgical wound infections.

Three of the 12 studies comparing parenteral administration with parenteral plus oral administration of antibiotics showed a statistically significant reduction in the incidence of surgical wound infection for those receiving the additional oral antibiotics.[28 48 49] However, two of these studies used inadequate parenteral antibiotics such as metronidazole alone,[48] or piperacillin alone.[28]

Oral neomycin plus erythromycin, given from nine to 20 hours before the operation, is a regimen commonly used in the United States. The main aim is to reduce the risk of bacterial contamination by reducing the bacteria in the large bowel. Some trials showed that oral neomycin and erythromycin on the day before surgery was effective, but further lowering of the rate of surgical wound infection may be achieved by adding parenteral antibiotics immediately before the operation.[50 51]

One RCT examined different methods of parenteral administration.[52] Patients received sulbactam and ampicillin either as a bolus injection, or bolus plus continuous infusion. The main aim of the trial was to assess concentrations of the drugs in different abdominal tissues. The sample size was too small to detect significant differences between the groups with regard to the number of surgical wound infections.

Adverse effects

Although toxicity and adverse effects are important issues for selecting prophylactic antimicrobials, these problems do not often occur with short term use. Over half of the identified trials measured and reported results of adverse effects after antibiotic prophylaxis in colorectal surgery. Skin rash, diarrhoea, and nausea were the most frequently reported adverse effects that may be attributable to the use of some antibiotic prophylaxis. Patients with a history of allergy to drugs were not included in the trials. No serious toxicity or adverse effects were reported except in one trial of latamoxef (Moxalactam), a drug which is not currently licensed in the UK.[53]

Risk factors of surgical wound infections

It was not possible to do a reliable analysis of risk factors from the trials included in the review because potential risk factors were inconsistently measured and findings might have been selectively reported. However, factors that were often reported in the included trials as being associated with an increased risk of surgical wound infection in colorectal surgery included duration of operation, obesity, the presence of drains, left-sided colonic resection, and inflammatory bowel disease. Two trials reported that the surgeon's experience can be a predictor of post-operative wound infection.[37 54] Perioperative blood trans-

fusion was also found to be associated with an increased risk of surgical wound infection in two trials.[36 39]

Contamination of the surgical wound by pathogenic organisms from both outside and inside the body is an important factor related to the risk of surgical wound infection, although it does not necessarily mean that infection will be inevitable.[55] Because a large volume of bacterial flora is contained in the large bowel, mechanical bowel cleansing is normally used before surgery.

The risk of surgical wound infection increases if the patient's resistance is compromised because of, for example, radiotherapy, corticosteroid treatment, chemotherapy, previous transplantation, diabetes, old age, obesity, or weight loss.[56] In addition, the patient's local resistance may be impaired because of interference with the blood supply at the operation site.[57]

Antibiotic resistance

A regimen of antibiotic prophylaxis in surgery may become ineffective because of the development of antibiotic resistant bacteria. The type and extent of antibiotic resistance varies "from country to country and among institutions within a country".[58] There is good evidence that inappropriate and over prescribing of antibiotics can increase the spread of resistant bacteria.[59] It has been suggested that the development of antibiotic resistant bacteria may be reduced if hospital infections could be prevented and if the use of antibiotics could be reduced.[60]

By preventing post-operative wound infection, a single dose or short term antibiotic prophylaxis can reduce the need for long term antibiotic treatment and therefore may contribute to reducing selection of antibiotic resistant bacteria. On the other hand, to be effective, prophylactic antibiotics should be chosen according to the local presence and prevalence of antibiotic resistant bacteria.[60] For these reasons, the search for the ideal prophylactic regimen must be a continuous process, and universal acceptance and use of any particular regimen should be avoided.[61]

Cost

Post-operative wound infections are costly for the NHS and its patients. The net cost of antimicrobial prophylaxis depends not only on the cost of the regimen (including the cost of drugs and the cost to prepare and administer) but also on the savings after using antibiotic prophylaxis, such as the savings due to a reduction in hospital stay. When there is no difference in the efficacy and safety of prophylactic antibiotics, the cost and ease of use are of great importance for the selection of regimens.[61 62]

It may be possible to reduce the cost of antibiotic prophylaxis without adversely affecting surgical wound infection rate.[63–67] This can be done, for example, by single dose or short term use (less than 24 hours after operation) instead of inappropriate long term use of antibiotics, and by using more effective and less costly drugs and routes of administration.

Surgical practice

Evidence from UK hospital surveys suggests that inappropriate use of antimicrobial prophylaxis is common. In one district hospital in England, major problems associated with the use of such drugs in abdominal and arterial surgery were identified. These included no antibiotics at the induction of anaesthesia, the use of questionable antibiotics both at induction of anaesthesia and post-operatively, and unnecessarily long post-operative administration of antibiotics. After the identification of these problems, guidelines were developed and, although the antibiotic regimen recommended may not have been optimal, the use of surgical antibiotic prophylaxis since their introduction became more appropriate. The cost of antimicrobial prophylaxis for each surgical patient was also reduced from £38.13 to £16.93.

A survey of guidelines for antimicrobial prophylaxis in surgery in 392 hospitals in the UK found that formal guidelines were available in only 47% of the 160 responding hospitals.[68] A more recent survey of existing antibiotic policies showed that cefuroxime (a second generation cephalosporin) plus metronidazole was the most frequently recommended policy.[7]

The *British National Formulary* currently recommends either a single dose of gentamicin plus metronidazole or cefuroxime plus metronidazole, given 2 hours before surgery for the prevention of infections after colorectal procedures.[69]

Existing guidelines and recommendations may still not be optimal, and continual evaluation of the appropriateness of the antimicrobial prophylaxis in surgical practice needs to be done at a local level.

Conclusions

The results of this review confirm that antibiotic prophylaxis is effective in the prevention of surgical wound infection in colorectal surgery. Although universal acceptance and use of a regimen should be avoided,[61] there are certain issues that should be considered when selecting an antimicrobial prophylaxis regimen for colorectal surgery:

- Antibiotics or antibiotic combinations should be active against both aerobic and anaerobic bacteria
- The administration of antibiotics should be timed to make sure that the tissue concentration of antibiotics around the wound area is sufficiently high when bacterial contamination occurs
- It appears that some regimens, such as metronidazole or piperacillin alone, may not be adequate. The effectiveness of many different regimens may be similar and it is difficult, if not impossible, to identify the best one
- Insufficient evidence exists to suggest that new generation cephalosporins are more effective than first generation cephalosporins

in preventing surgical wound infection after colorectal surgery

- Single dose regimens have been shown to be as effective as multiple dose regimens for the prevention of surgical wound infections, and are likely to be associated with less toxicity, fewer adverse events, less risk of developing bacterial resistance, and lower costs.

The development of bacterial resistance may be reduced by the appropriate use of antimicrobial prophylaxis in colorectal surgery because the prevention of surgical wound infections will reduce the need for long term, postoperative, antibiotic treatment. The use of single dose rather than multiple dose regimens, and the use of established antibiotics instead of new drugs should be encouraged, providing efficacy is not impaired.

Future research should focus on the understanding of the practical use of antimicrobial prophylaxis in colorectal surgery in the UK and the cost effectiveness of different regimens of antibiotic prophylaxis. Based on the best available research evidence, guidelines should be developed locally by surgeons, microbiologists, and pharmacists, taking into account local resistance profiles to achieve more cost effective use of antimicrobial prophylaxis in colorectal surgery. Such guidelines should be constantly reviewed and updated because no definitive version can be established.

1 Song F, Glenny A. Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials. *Br J Surg* 1998;**85**:1232–41.
2 Song F, Glenny A. Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials. *Health Technol Assessment*, 1998;**2**:7.
3 McGuigan S. *OHE compendium of health statistics.* 10th edition. London: Office of Health Economics, 1997.
4 Dellinger E, Gross P, Barrett T, *et al*. Quality standard for antimicrobial prophylaxis in surgical procedures. *Clin Infect Dis* 1994;**18**:422–7.
5 McGowan J. Cost and benefit of perioperative antimicrobial prophylaxis: methods for economic analysis. *Rev Infect Dis* 1991;**13**:879–89.
6 Ludwig K, Carlson M, Condon R. Prophylacitc antibiotics in surgery. *Annu Rev Med* 1993;**44**:385–93.
7 Bloxham C. *Towards evidence-based antibiotic prescribing: A national survey of antibiotic policies*. MBA degree, 1997.
8 Gorbach S, Condon R, Conte J, *et al*. Evaluation of new anti-infective drugs for surgical prophylaxis. *Clin Infect Dis* 1992;**15**:S313–38.
9 Standing Medical Advisory Committee, Subgroup on Antimicrobial Resistance. *The path of least resistance*. London: Department of Health, 1998.
10 Baum M, Anish D, Chalmers T, *et al*. A survey of clinical trials of antibiotic prophylaxis in colon surgery: evidence against further use of no-treatment controls. *N Engl J Med* 1981;**305**:795–9.
11 Gomez-Alonso A, Lozano F, Perez A, *et al*. Systemic prophylaxis with gentamicin-metronidazole in appendicectomy and colorectal surgery: a prospective controlled clinical study. *Int Surg* 1984;**69**:17–20.
12 Gottrup F, Diederich P, Sorensen K, *et al*. Prophylaxis with whole gut irrigation and antimicrobials in colorectal surgery. A prospective, randomized double-blind clinical trial. *Am J Surg* 1985;**149**:317–21.
13 Schiessel R, Huk I, Wunderlich M, *et al*. Postoperative infections in colonic surgery after enteral bacitracin-neomycin-clindamycin or parenteral mezlocillin-oxacillin prophylaxis. *J Hosp Infect* 1984;**5**:289–97.
14 Utley R, Macbeth W. Preoperative cefoxitin: a double-blind prospective study in the prevention of wound infections. *J R Coll Surg Edinb* 1984;**29**:143–6.
15 Roland M. Prophylactic regimens in colorectal surgery: An open, randomised, consecutive trial on metronidazole used alone or in combination with ampicillin or doxycyline. *World J Surg* 1986;**10**:1003–8.
16 Haverkorn M. Peroperative systemic prophylaxis in colorectal surgery. *Drugs Exp Clin Res* 1985;**11**:111–14.
17 Claesson B, Filipsson S, Holmlund D, *et al*. Selective cefuroxime prophylaxis following colorectal surgery based on intra-operative dipslide culture. *Br J Surg* 1986;**73**:953–7.
18 Lindhagen J, Andaker L, Hojer H. Comparison of systemic prophylaxis with metronidazole/placebo and metronidazole/fosfomycin in colorectal surgery. *Acta Chir Scand* 1984;**150**:317–23.
19 Jagelman D, Fazio V, Lavery I, *et al*. A prospective, randomized, double-blind study of 10% mannitol mechanical bowel preparation combined with oral neomycin and short-term, perioperative, intravenous flagyl as prophylaxis in elective colorectal resections. *Surgery* 1985;**98**:861–5.
20 Desaive C. Utilisation de la ticarcilline et/ou de la gentamicine dans la propylaxie de l'infection en chirurgie recto-colique: etude randomisee. *Acta Ther* 1985;**11**:405–15.
21 Gerner T, Nygaard K, Kaaresen R, *et al*. Antibiotic prophylaxis in colorectal surgery. Combined doxycycline-tinidazole vs. doxycycline alone. *Acta Chir Scand* 1989;**155**:121–4.
22 Bergman L, Solhaug J. Single-dose chemoprophylaxis in elective colorectal surgery. A comparison between doxycycline plus metronidazole and doxycycline. *Ann Surg* 1987;**205**:77–81.
23 Hakansson T, Raahave D, Hansen O, *et al*. Effectiveness of single dose prophylaxis with cefotaxime and metronidazole compared with three doses of cefotaxime alone in elective colorectal surgery. *Eur J Surg* 1993;**159**:177–80.
24 University of Melbourne Colorectal Group. Clinical trial of prophylaxis of wound sepsis in elective colorectal surgery comparing ticarcillin with tinidazole. *Aust N Z J Surg* 1986;**56**:209–13.
25 University of Melbourne Colorectal Group. Systemic Timentin is superior to oral tinidazole for antibiotic prophylaxis in elective colorectal surgery. *Dis Colon Rectum* 1987;**30**:786–9.
26 The Norwegian Study Group for Colorectal Surgery. Should antimicrobial prophylaxis in colorectal surgery include agents effective against both anaerobic and aerobic microorganisms? A double-blind, multicenter study. *Surgery* 1985;**97**:402–7.
27 Reynolds J, Jones J, Evans D, *et al*. Do preoperative oral antibiotics influence sepsis rates following elective colorectal surgery in patients receiving perioperative intravenous prophylaxis? *Surg Res Comm* 1989;**7**:71–7.
28 Taylor E, Lindsay G, and the West of Scotland Surgical Infection Study Group. Selective decontamination of the colon before elective colorectal surgery. *World J Surg* 1994;**18**:926–32.
29 Antonelli W, Borgani A, Machella C, *et al*. Comparison of two systemic antibiotics for the prevention of complications in elective colorectal surgery. *Ital J Surg Sci* 1985;**15**:255–8.
30 Jones R, Wojeski W, Bakke J, *et al*. Antibiotic prophylaxis of 1036 patients undergoing elective surgical procedures: a prospective randomized comparative trial of cefazolin, cefoxitin and cefotaxime in a prepaid medical practice. *Am J Surg* 1987;**153**:341–6.
31 Lumley J, Siu S, Pillay S, *et al*. Single dose ceftriaxone as prophylaxis for sepsis in colorectal surgery. *Aust N Z J Surg* 1992;**62**:292–6.
32 Plouffe J, Perkins R, Fass R, *et al*. Comparison of the effectiveness of moxalactam and cefazolin in the prevention of infection in patients undergoing abdominal operations. *Diagn Microbiol Infect Dis* 1985;**3**:25–31.
33 Thomas W, Cooper M, Holt A, *et al*. Latamoxef: single agent prophylaxis in colorectal surgery. *J Antimicrob Chemother* 1985;**16**:121–8.
34 Sanderson P. Antimicrobial prophylaxis in surgery: microbiological factors. *J Antimicrob Chemother* 1993;**31**(suppl):1–9.
35 Culver D, Horan T, Gaynes R, *et al*. Surgical wound infection rates by wound class, operative procedure, and patient risk index. *Am J Med* 1991;**91**:152S-7S.
36 Jensen L, Anderson A, Fristrup S, *et al*. Comparison of one dose versus three doses of prophylactic antibiotics, and the influence of blood transfusion, on infectious complications in acute and elctive surgery. *Br J Surg* 1990;**77**:513–18.
37 Cuthbertson A, McLeish A, Penfold J, *et al*. A comparison between single dose and double dose intravenous timentin for the prophylaxis of wound infection in elective colorectal surgery. *Dis Colon Rectum* 1991;**34**:151–5.
38 Carr N, Hobbiss J, Cade D, *et al*. Metronidazole in the prevention of wound sepsis after elective colorectal surgery. *J R Coll Surg Edinb* 1984;**29**:139–42.
39 Stewart M, Taylor E, Lindsay G, and the West of Scotland Surgical Infection Study Group. Infection after colorectal surgery: A randomized trial of prophylaxis with piperacillin versus sulbactam/piperacillin. *J Hosp Infect* 1995;**29**:285–90.
40 Bartlett S, Burton R. Effects of prophylactic antibiotics on wound infection after elective colon and rectal surgery. *Am J Surg* 1983;**145**:300–9.
41 Raahave D, Hesselfeldt P, Pedersen T. Cefotaxime intravenous versus oral neomycin-erythromycin for prophylaxis of infections after colorectal operations. *World J Surg* 1988;**12**:369–73.
42 Raahave D, Hesselfeldt P, Pedersen T, *et al*. No effect of topical ampicillin prophylaxis in elective operations of the colon or rectum. *Surg Gynecol Obstet* 1989;**168**:112–14.
43 Moesgaard F, Nielsen M, Hjortrup A, *et al*. Intraincisional antibiotic in addition to systemic antibiotic treatment fails to reduce wound infection rates in contaminated abdominal surgery. A controlled clinical trial. *Dis Colon Rectum* 1989;**32**:36–8.
44 Moesgaard F, Nielsen M. Failure of topically applied antibiotics, added to systemic prophylaxis, to reduce perineal wound infection in abdominoperineal excision of the rectum. *Acta Chir Scand* 1988;**154**:589–92.

45 Juul P, Merrild U, Kronborg O. Topical ampicillin in addition to a systemic antibiotic prophylaxis in elective colorectal surgery: A prospective randomized study. *Dis Colon Rectum* 1985;**28**:804–6.
46 Greig J, Morran C, Gunn R, *et al*. Wound sepsis after colorectal surgery: the effect of cefotetan lavage. *Chemioterapia* 1987;**6**(suppl):595–6.
47 Quendt J, Blank I, Seidel W. Perioperative antibiotic prophylaxis by transperitoneal and subcutaneous application during elective colorectal surgery. A prospective randomized comparative study. *Langenbecks Arch Chir* 1996; **381**:318–22.
48 Khubchandani I, Karamchandani M, Sheets J, *et al*. Metronidazole versus erythromycin, neomycin, and cefazolin in prophylaxis for colonic surgery. *Dis Colon Rectum* 1989;**32**: 17–20.
49 McArdle C, Moran C, Pettit L, *et al*. Value of oral antibiotic prophylaxis in colorectal surgery. *Br J Surg* 1995;**82**:1046–8.
50 Lau W, Chu K, Poon G, *et al*. Prophylactic antibiotics in elective colorectal surgery. *Br J Surg* 1988;**75**:782–5.
51 Schoetz D, Roberts P, Murray J, *et al*. Addition of parenteral cefoxitin to regimen of oral antibiotics for elective colorectal operations. *Ann Surg* 1990;**212**:209–12.
52 Martin C, Cotin A, Giraud A, *et al*. Comparison of concentrations of sulbactam-ampicillin administered by bolus injections or bolus plus continuous infusion in tissues of patients undergoing colorectal surgery. *Antimicrob Agents Chemother* 1998;**42**:1093–7.
53 Morris D, Fabricius P, Ambrose N, *et al*. A high incidence of bleeding is observed in a trial to determine whether addition of metronidazole is needed with latamoxef for prophylaxis in colorectal surgery. *J Hosp Infect* 1984;**5**:398–408.
54 University of Melbourne Colorectal Group. A comparison of single-dose systemic Timentin with mezlocillin for prophylaxis of wound infection in elective colorectal surgery. *Dis Colon Rectum* 1989;**32**:940–3.
55 McDonald P, Finlay-Jones J. Microbial evolution of surgical infection. In: Watts JM, McDonald P, O'Brien PE, *et al*, editors. *Infection in surgery: basic and clinical aspects*. Edinburgh: Churchill Livingstone, 1981.
56 Martin C. Antimicrobial prophylaxis in surgery: general concepts and clinical guidelines. *Infect Control Hosp Epidemiol* 1994;**15**:463–71.
57 Burke J. Current perspectives of surgical infection. In: Watts JM, McDonald P, O'Brien PE, *et al*, editors. *Infection in surgery: basic and clinical aspects.* Edinburgh: Churchill Livingstone, 1981.
58 Gold H, Moellering R. Antimicrobial-drug resistance. *N Engl J Med* 1996;**335**:1445–54.
59 Department of Health. *Hospital episode statistics (HES) and population data provided by the statistics division*. London: DOH, 1996.
60 Office of Technology Assessment (US Congress). *Impact of antibiotic-resistant bacteria*. Washington DC: US Government Printing Office, 1995.
61 Norrby S. Cost effective prophylaxis of surgical infections. *Pharmacoeconomics* 1996;**10**:129–39.
62 Fry D. Antibiotics in surgery. An overview. *Am J Surg* 1988; **155**:11–15.
63 Scalley R, Irwin A, Poduska P, *et al*. Surgical antibiotic prophylaxis, patient morbidity, and cost reduction: a three year study. *Drug Intell Clin Pharm* 1987;**21**:648–52.
64 Scher K, Bernstein J, Arenstein G, *et al*. Reducing the cost of surgical prophylaxis. *Am J Surg* 1990;**56**:32–5.
65 Dobrzanski S, Lawley D, McDermott I, *et al*. The impact of guidelines on peri-operative antibiotic administration. *J Clin Pharm Ther* 1991;**16**:19–24.
66 Davey P, Vacani P, Parker S, *et al*. Assessing cost effectiveness of antimicrobial treatment: monotherapy compared with combination therapy. *Eur J Surg* 1994; **573**(suppl):67–72.
67 Evans R, Pestotnik S, Burke J, *et al*. Reducing the duration of prophylactic antibiotic use through computer monitoring of surgical patients. *Drug Intell Clin Pharm* 1990;**24**:351–4.
68 Widdison A, Pope N, Brown E. Survey of guidelines for antimicrobial prophylaxis in surgery. *J Hosp Infect* 1993;**25**: 199–205.
69 *British National Formulary*. London: British Medical Association and the Royal Pharmaceutical Society, March 1998.