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Effective Health Care

Bulletin on the effectiveness of health service interventions for decision makers

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Antimicrobial prophylaxis in colorectal surgery

- Antimicrobial prophylaxis is effective for the prevention of surgical wound infections in colorectal surgery and should be used.
- No 'gold standard' regimen can be identified. There is no difference in the rate of surgical wound infections between many different regimens, though certain regimens appear to be inadequate.
- Single dose regimen may be as effective as multiple dose regimen and have related cost benefits.
- Guidelines based on existing evidence should take into account local prevalence of pathogens and resistance profiles in order to achieve more cost-effective use of antimicrobial prophylaxis in colorectal surgery.
- Appropriate use of antimicrobial prophylaxis in colorectal surgery may help to reduce the development of antibiotic resistant bacteria.
- Despite adverse publicity concerning the use of antibiotics, GP's should advise patients being referred for colorectal surgery that the appropriate use of antimicrobial prophylaxis can reduce the risk of surgical wound infections.

The contents of this bulletin are likely to be valid for around one year, by which time significant new research evidence may have become available.

A. Background

Hospital-acquired infections occur in about 1 in 10 hospitalised patients.[1] These infections increase morbidity and mortality, prolong hospital stay and increase the cost of medical care.[2,3] Surgical wound infections are among the most common hospital-acquired infections, accounting for around 23%.[1] In 1993 it was estimated that hospital-acquired infections occurring in surgical patients cost the NHS over £170 million in England alone.[4]

Contamination by bacteria from the contents of the large bowel means that colorectal surgery is associated with a particularly high risk of surgical wound infection. If antimicrobial prophylaxis is not used, about 40% of patients develop wound infections after colorectal surgery.[5] This figure is reduced to around 11% when patients receive some form of antimicrobial prophylaxis.[6,7]

ANTIMICROBIAL PROPHYLAXIS - the administration of antimicrobial agents (antibiotics) as a preventive measure, i.e. before the onset of infection.

Over the past 20 years, the practice of using antimicrobial prophylaxis before surgery has increased greatly, with such antimicrobial agents accounting for about half of all antibiotics prescribed in hospitals.[8] There is uncertainty, however, about which drugs should be used, and about the most effective timing, duration and route of administration.[9] In addition, the contribution of inappropriate prescribing to the spread of antimicrobial resistance must be considered.[10]

A recent survey of antibiotic policies examined 68 sets of guidelines from hospitals across the UK, highlighting the variation in recommended prophylactic regimens.[8] Some hospitals appear to have no set policy for the prescription of antimicrobial prophylaxis before colorectal surgery, or surgery in general. Consequently, the choice of antibiotic regimen may be less than optimal.

This issue of *Effective Health Care* summarises and updates the findings of a systematic review examining the effectiveness of different antimicrobial regimens used for the prevention of surgical wound infection in patients undergoing colorectal surgery.[6,7] A summary of the review methodology is included in the appendix of this bulletin.

B. Effectiveness

B.1 Antibiotics versus no antibiotics: As wound contamination by pathogenic bacteria is common and host resistance is often defective, antibiotic prophylaxis should play an important role 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.[11] However, since then, four randomised controlled trials (RCTs) which did use a 'no-antibiotic' control group and met the inclusion criteria for this bulletin, have been published.[12–15] All showed a greatly reduced surgical wound infection rate in the antibiotic group (12.9% versus 40.2%; pooled OR 0.24; 95% CI: 0.13, 0.43) (see Fig. 1). This demonstrates that antimicrobial prophylaxis for colorectal surgery is effective and should be used.

B.2 Choice of antimicrobial regimen: More than 70 different antibiotic regimens were tested in the 152 identified trials (147 included in the original review,[6] five additional trials identified during an update of the review[16–20]). Some of the more frequently assessed antibiotics and antibiotic combinations are listed in Table 1. The overall rate of surgical wound infection for all patients who received antibiotics was 11.1% (n = 23,751).

It was not possible to identify an optimal antimicrobial prophylaxis regimen. The estimates of effectiveness are 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.

The safety profile and relatively broad spectrum of the cephalosporins make them a popular choice for the prevention of surgical wound infections.[21] A comparison between first-generation cephalosporins and the new-generation (second- and third-generation) cephalosporins was undertaken in six trials (reported in five articles).[22–26] No statistically significant differences between groups were demonstrated in any of the trials. Pooling of the results from the six trials showed no statistically significant difference between the first-generation and new-generation cephalosporins (overall rate of surgical wound infection: 6.0% versus 6.4%; OR 0.93; 95% CI: 0.46, 1.86).

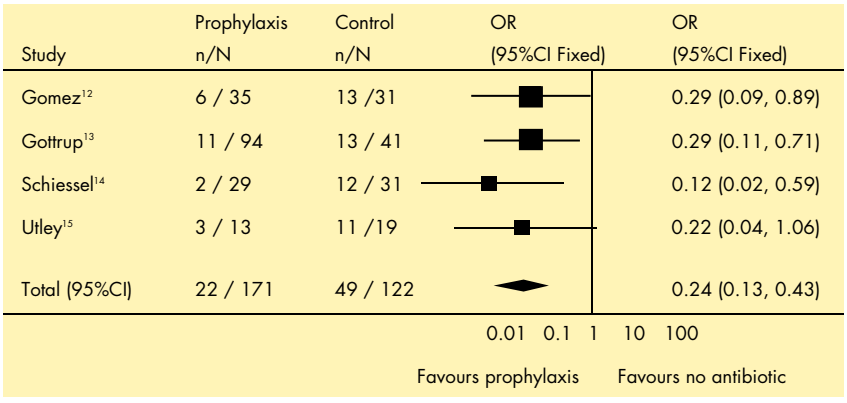


Fig. 1 Antibiotic prophylaxis versus no antibiotic control

B.3 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,[13] doxycycline,[29] cefuroxime,[30,31] netilmicin[30] or fosfomycin.[32] This is because metronidazole is active against anaerobic bacteria but ineffective against aerobic bacteria. Metronidazole, therefore, should be combined with other antibiotics that are active against aerobic bacteria, as both kinds of micro-organisms are present in the bowel.

Table 1 Frequently assessed antibiotics included in the review[6,7]

No. of trials	Antibiotics	No.of trials	Antibiotics
9	Ampicillin+Metronidazole	20	Cefuroxime+Metronidazole
4	Aztreonam+Clindamycin	5	Ciprofloxacin+Metronidazole
6	Cephazolin+Metronidazole	9	Co-amoxiclav
11	Cefotaxime+Metronidazole	5	Gentamicin+Clindamycin
10	Cefotaxime	15	Gentamicin+Metronidazole
9	Cefotetan	5	Mezlocillin+Metronidazole
8	Cefoxitin+Neomycin+Erythromycin	7	Mezlocillin
22	Cefoxitin	10	Neomycin+Erythromycin
8	Ceftriaxone+Metronidazole	4	Netilmicin+Metronidazole
5	Ceftriaxone	5	Ticarcillin+Clavulanic acid

Note: Inclusion of agents in this list does not necessarily mean that the regimen is recommended. For example, 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 prior to the operation.[27,28]

The following antibiotics used on their own were shown to be inadequate at preventing surgical wound infection: metronidazole,[13,29,32] neomycin,[33] gentamicin,[34] doxycycline,[35,36] cefotaxime,[37] tinidazole[38-40] and piperacillin.[41,42] These studies imply that any prophylactic regimen chosen for colorectal surgery should include broad spectrum cover for both aerobic and anaerobic organisms.

B.4 Timing and duration of administration: By definition, prophylactic use of antimicrobial agents means administration before the onset of infection. Once infection occurs, antibiotic administration should be considered as therapeutic. To prevent postoperative infection, it is crucial that the concentration of antibiotics in the tissue surrounding the surgical wound is sufficient at the time of bacterial contamination.[5,43] The half-life of antimicrobial agents and their distribution in different tissues varies greatly between agents.[44] These factors need to be considered when assessing the timing and number of doses required for each antimicrobial agent.

Seventeen trials included in the review compared a single-dose with a multiple-dose regimen, using the same antibiotic or combination of antibiotics.[6,7] None of these trials found a significant difference in postoperative surgical wound infection rate between the two regimens. Pooling of the results from the 17 trials again showed a non-significant difference between single and multiple dose regimens (10.6% versus 9.7%; OR 1.17; 95% CI: 0.89, 1.54).

There is no evidence to suggest that continuing to administer 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 operation is associated with a higher rate of surgical wound infection.[45] However, trials comparing single and multiple-dose regimens and reporting duration of operations were unable to provide any convincing evidence about the relationship between the efficacy of different dose regimens and the duration of operation.[46-48] Clinicians need to consider additional factors associated with an increased incidence of infection (see section C) to decide whether a second dose is required when surgical procedures last longer than 2 hours.

B.5 Route of administration: Prophylactic antibiotics can be given by three routes:[49]

i) via the gastrointestinal system – by mouth, rectum, colostomy, or nasogastric tube;

ii) parenteral route – by subcutaneous, intramuscular or intravenous injection;

iii) topical administration – application directly to the surgical wound at the time of operation.

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 the parenteral route alone with the parenteral plus topical use of antimicrobial prophylaxis.[50–55] One study compared parenteral administration with an intraoperative intraperitoneal plus subcutaneous application.[20] Both groups received the same antimicrobial agent (cephazolin). Serum concentrations at one and two hours postoperatively were statistically significantly higher in patients receiving the topical application, but no significant difference was demonstrated with regard to surgical wound infections.

Three of the 12 studies comparing parenteral administration with parenteral plus oral administration of antibiotics demonstrated a statistically significant reduction in the incidence of surgical wound infection for those receiving the additional oral antibiotics.[42,56,57] However, two of these studies used inadequate parenteral antibiotics such as piperacillin alone,[42] or metronidazole alone.[56]

Oral neomycin plus erythromycin, given from 9 to 20 hours before the operation, is a regimen commonly used in the US. 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 prior to the operation.[27,28]

One RCT examined different methods of parenteral administration.[58] 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.

B.6 Adverse effects: Although toxicity and adverse effects are important issues for selecting prophylactic antimicrobials, these problems do not occur often with short term use. Over half of the identified trials measured and reported adverse effects after antibiotic prophylaxis in colorectal surgery.[6] 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.[59]

C. Risk factors

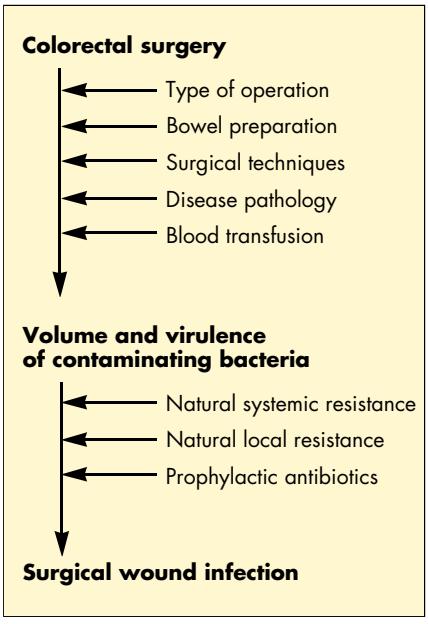
Factors associated with bacterial contamination and patient's own resistance will also be associated with the risk of surgical wound infection (see Box 1).

It is not possible to carry out 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 postoperative wound infection.[47,60] Perioperative blood transfusion was also found to be associated with an increased risk of surgical wound infection in two trials.[46,61]

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, though it does not necessarily mean that infection will be inevitable.[62] Because a large volume of bacterial flora is contained in the large bowel, mechanical bowel cleansing (for example, the use of bowel cleansing liquids) is normally used before elective colorectal surgery.

The risk of surgical wound infection also increases if the patient's natural resistance is compromised because of, for example, radiotherapy, corticosteroid therapy, chemotherapy, previous transplantation, diabetes, old age, obesity or weight loss,[44] or because of interference with the blood supply at the operation site.[63]

Box 1 Factors influencing the occurrence of surgical wound infections in colorectal surgery



D. Bacteriology and antibiotic resistance

Most trials reported results of bacteriological testing of organisms from wound infections (110/134).[6,7] Bacteria isolated from infected wounds in colorectal surgery were usually a mix of aerobic and anaerobic flora among which *Escherichia coli* and *Bacteroides fragilis* were most common. *Staphylococcus aureus* was also often isolated. The type of bacteria isolated from surgical wound infection can be altered by antibiotic prophylaxis. For example, bacteria isolated from wound infections were predominantly aerobic bacteria when prophylactic metronidazole, which is active against anaerobic but not aerobic organisms, was used.[31] One trial found that anaerobes were isolated from only 1 of 15 wound infections in patients who received metronidazole but from 3 of 6 wound infections in patients who received cephazolin plus oral neomycin and erythromycin.[56]

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'.[64] There is good evidence that inappropriate and over-prescribing of antibiotics can

increase the spread of resistant bacteria.[65] 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.[66]

By preventing postoperative wound infection, single dose or short-term antibiotic prophylaxis can reduce the need for long-term antibiotic therapy 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.[66] 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.[67]

E. Cost

Postoperative wound infections are costly for the NHS and patients. Both costs and benefits of antimicrobial prophylaxis in surgery may be direct or indirect, and a number of components may be included.[3] Costs of antibiotic prophylaxis include costs of antibiotics, equipment and staff time. These may be offset to some extent by reductions in the length of the hospital stay. Although this review has not attempted a systematic review of the cost-effectiveness of antimicrobial prophylaxis in colorectal surgery, general comments can be made.

The risk of postoperative wound infection is high in colorectal surgery if antimicrobial prophylaxis is not employed, and surgical wound infection is associated with a prolonged hospitalisation and costly antibiotic treatment. For example, one study observed that superficial surgical wound infection prolonged hospital stay by an average of 12.6 days.[68] A study in Scotland found that the median cost to the hospital of a wound infection after colorectal surgery in 1990 was £978 (95% CI: £484, £1521).[69] A US study found that, compared to a control group, prophylactic gentamicin plus metronidazole resulted in a lower rate of surgical wound infection and saved $406 per patient of colorectal surgery.[12]

The net cost depends not only on the cost of the regimen (including the cost of drugs and their preparation and administration) but also the savings after using antibiotic prophylaxis, such as those due to reduced hospital stay. When there is no difference in the efficacy and safety of prophylactic antibiotics, the cost and ease of use are key in the selection of regimens.[67,70]

It may be possible to reduce the cost of antibiotic prophylaxis without adversely affecting surgical wound infection rates.[71–75] 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.

F. 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 antimicrobial prophylaxis in abdominal and arterial surgery were identified.[73] These included no antibiotics at the induction of anaesthesia, missed doses postoperatively, inappropriate antibiotic combinations, different antibiotics given and unnecessarily long postoperative administration of antibiotics. Following the identification of these problems, guidelines were developed (one perioperative and two postoperative doses of cefotaxime (1g) plus metronidazole (500mg) intravenously in addition to bowel preparation with oral neomycin (1g) plus metronidazole (400mg)) and the use of surgical antibiotic prophylaxis following their introduction became more appropriate. The cost of antimicrobial prophylaxis was also reduced from £38 to £17 per patient.[73]

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.[76] Regimens recommended in the existing guidelines for colorectal surgery included co-amoxiclav (6%), second-generation cephalosporins (2%), metronidazole alone (4%), aminoglycosides plus metronidazole (19%), first-generation cephalosporins plus metronidazole (15%), second-generation cephalosporins plus metronidazole (42%), and other antibiotics (12%). Of the recommended regimens, 6% used antibiotics which did not provide cover against both aerobic and anaerobic bacteria.

A more recent survey of UK antibiotic policies demonstrated a similar pattern, with cefuroxime (a second-generation cephalosporin) plus metronidazole being the most frequently recommended policy.[8] The British National Formulary currently recommends either a single dose of gentamicin plus metronidazole or cefuroxime plus metronidazole, given in the 2 hours before surgery for the prevention of infections after colorectal procedures.[77]

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 carried out at a local level.

G. Implications

Antibiotic prophylaxis is effective in the prevention of surgical wound infection in colorectal surgery. Although universal acceptance and use of a fixed regimen should be avoided,[67] 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 very difficult, if not impossible, to identify the best one.
- There is insufficient evidence to suggest that new-generation cephalosporins are more effective than first-generation cephalosporins in preventing surgical wound infection following colorectal surgery.
- Single-dose regimens have been demonstrated 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 therapy. 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 in order to achieve more cost-effective use of antimicrobial prophylaxis in colorectal surgery. Such guidelines should be regularly reviewed and updated, since no definitive version can be established.

Appendix on research methods

Searches of computerised databases (including MEDLINE, EMBASE, and the Cochrane Controlled Trials Register) were conducted to identify randomised controlled trials (RCTs) published between 1984 and July 1998. The year 1984 was chosen due to: changes in clinical use of antimicrobial prophylaxis; the introduction of many new antibiotics; improvements in surgical procedures; possible emergence of antibiotic-resistant micro-organisms, and; the large volume of literature in this area. Bibliographies of reviews and all identified trials were examined, and a sample of key journals handsearched to locate additional studies. All languages were considered.

The relevance and validity of each study were assessed and data extracted by one reviewer and independently checked by another. Data from individual studies were extracted using a pre-defined form and managed using an Idealist database. When insufficient data were available, authors of the primary studies were contacted for clarification. Indicators of study quality included method of randomisation, blind outcome assessment, written definition of surgical wound infection, description of withdrawals and an a priori calculation of sample size.

The wound itself has the greatest risk of infection from endogenous bacterial contamination during surgical procedures.[78] Therefore, the rate of surgical wound infection was chosen as the principal outcome measure to assess the relative effectiveness of antimicrobial prophylaxis in colorectal surgery. Where possible, only abdominal wound infections were assessed. However, it was not always clear whether data on perineal wound infections were included in the results. Data on other postoperative infections (systemic and remote infections), duration of hospital stay, cost of medical care, mortality and side-effects were also collected from each trial where available.

Studies were grouped according to the antibiotic used. Formal meta-analysis was often inappropriate due to heterogeneity amongst trials. Data synthesis, therefore was predominantly qualitative. When meta-analysis was appropriate, MetaView in the Cochrane Review Manager Software (RevMan, version 3.0 for Windows) was used. The Mantel-Haenszel method was chosen for calculating overall odds ratios and the chi-squared method for testing heterogeneity between individual studies.

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