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THE USE OF PROPHYLACTIC ANTIMICROBIALS IN GASTROINTESTINAL SURGERY

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Gastrointestinal cerrahide profilaktik antimikrobiyal kullanımı.

CONTENTS

INTRODUCTION

Sepsis despite the wide range of available antibiotics remains as one of the most important causes of postoperative morbidity. The principal complications include wound sepsis, intra-abdominal or pelvic abscess and septicaemia. The consequences of these potentially preventable and sometimes fatal complications in gastrointestinal surgery include thromboembolism, malnutrition, anastomotic dehiscence, wound disruption, disseminated intravascular coagulation and death.

Prophylactic antibiotics should only be used either when there is a high risk of sepsis or where sepsis, although rare, is associated with life-threatening consequences. Operations carrying a potentially high risk of sepsis are those on the gastrointestinal tract (13). It is preferable to recommend antibiotic prophylaxis only when these measures have been proved to be of value by well conducted randomised control trials (7).

The term prophylaxis must be distinguished from antibiotic therapy. The word prophylaxis is only appropriate when there has been no preoperative contamination or established infection of tissues. For this reason, antibiotics used in the treatment of traumatic wounds established sepsis and acute disease are not prophylactic and will not be considered in detail in this article.

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PRE-OPERATIVE PREPARATION AND SURGICAL TECHNIQUE

Antibiotic prophylaxis cannot be expected to succeed if there is pre-existing sepsis in a patient having an elective operation as when there are staphylococcal or skin lesions or an upper respiratory tract infection. Such patients should have their operations deferred until the episode of co-existing infection has resolved. Antimicrobial prophylaxis should not be considered a substitute for poor surgical technique. There is always an increased risk of sepsis if there has been inadequate haemostasis, if non-absorbable suture material (particularly large sutures) have been used, if the blood supply to tissues has been compromised and when open drains have been used (10,11).

There is no evidence that wound protection with adhesive drapes reduces the incidence of post-operative sepsis from exogenous bacteria (41). Whenever a hollow viscus containing bacteria (for example the colon) is opened, this allows a much greater number of bacteria to enter the wound than from the skin. It is important that the colon should have been efficiently cleared of faecal material by mechanical bowel preparation before colorectal operations since there is a high risk of anastomotic dehiscence and secondary intra-abdominal sepsis if the colon has been inadequately prepared, even though prophylactic antimicrobials may have been used (25). The same principle also applies to patients with gastric outlet obstruction in which case pre-operative gastric lavage is indicated.

PRINCIPLES OF PERI-OPERATIVE ANTIBIOTIC PROPHYLAXIS

The rationale behind antimicrobial prophylaxis is that a high dose of antibiotic should be presented to the tissues and to the circulation at the time when bacteria are released into the surgical field (5). The antibiotic should be bactericidal.

There are three possible routes for administering antimicrobial prophylaxis: a) by the oral route, b) topically in the peritoneal cavity or the wound, and c) by systemic prophylaxis. Administration of oral agents with mechanical bowel preparation has been the traditional method for prophylaxis in elective colorectal surgery. Many of the earlier antimicrobials such as neomycin and phthalysulphathiazole are ineffective against the faecal anaerobes and therefore have not reduced the frequency of postoperative sepsis. More recently combinations of neomycin and erythromycin or neomycin and metronidazole have been shown to reduce the faecal flora of the colon and have also to some extent reduced the incidence of post-operative sepsis. However, oral agents have their own disadvantages; they increase the risk of bacterial resistance, allow overgrowth of staphylococci and have been implicated as a cause of pseudomembranous colitis (28). Topical antibiotics placed in the wound are capable of reducing the incidence of wound sepsis but have been shown to be inferior to systemic prophylaxis because they do not protect against intra-abdominal abscess and septicaemia. Intraparietal antibiotics have not been adequately evaluated for prophylaxis though a recent study from our Unit suggested that tetracycline lavage might have a small advantage if used in addition to systemic antibiotic cover (44). The best method of achieving effective antimicrobial prophylaxis is to give a very large dose of antibiotic with a long half life by the intravenous route. The antibiotic should be administered immediately prior to operation, preferably in the anaesthetic room, before endogenous bacteria have been released at operation. Higgins and others (1980) showed even in colorectal surgery that it is quite unnecessary to prolong antibiotic prophylaxis for 5 days (23). Systemic administration also provides predictable serum levels which is an advantage over topical, intrarectal or oral agents.

RISKS OF ANTIMICROBIAL PROPHYLAXIS

There are very few dangers in using systemic antimicrobial prophylaxis provided that only one dose of a systemic agent is used. It is only when antimicrobial prophylaxis becomes prolonged that complications arise. Potential complications include antibiotic resistance, superinfection, pseudomembranous colitis and toxicity. Some examples of specific toxic complications include: nephrotoxicity to cephaloridine or ototoxicity following aminoglycoside administration, bleeding after certain broad spectrum cephalosporins: anaphylaxis with certain of the penicillins and cephalosporins, the effects of aminoglycosides on non-depolarising muscle relaxants, blood dyscrasia following administration of chloramphenicol or cotrimoxazole and severe diarrhoea after certain broad spectrum antimicrobials.

SOURCE OF POST-OPERATIVE SEPSIS

Bacterial contamination at operation can usefully be classified as exogenous or endogenous. Exogenous sepsis is usually staphylococcal unless the wound is in the groin or near the perineum in which case intestinal organisms are often responsible.

The source of bacteria responsible for endogenous sepsis include the female genital tract, the lower urinary tract and the intestine. Intra-operative contamination from the large bowel and the vagina is inevitable whenever these organs are opened. Contamination by bacteria from the upper gastrointestinal tract, bile and urine depends on the underlying pathology.

ORGANISMS RESPONSIBLE FOR ENDOGENOUS SEPSIS

a) Oropharynx

The oropharynx is always colonised by modest numbers of oral anaerobes and streptococci.

b) Stomach

The stomach contents are usually sterile in normal patients, or in those with hypersecretion of acid. Gastric contents are heavily colonised by staphylococci, oral streptococci, oral anaerobes and *Escherichia coli* if there is hypochlorhydria, as in patients with gastric ulcer, gastric cancer, patients receiving cimetidine and in those with post-operative alkaline reflux and patients with pernicious anaemia. The median counts of bacteria colonising the stomach are shown on Table 1, the highest counts being found in gastric cancer patients after gastrectomy and after H^2 antagonist agents. Detailed analysis of hypochlorhydric patients indicates that *B. fragilis* is recovered from over a third of cases of gastric carcinoma and that clostridia are present in about a quarter of these patients (Table 2).

Table 1. Median counts of bacteria in fasting gastric juice (log 10) (Author's series).

27 Normal subjects	$1x10^1$
51 Duodenal ulcer	$4x10^1$
30 Gastric ulcer	$7x10^4$
56 Gastric cancer	$2x10^7$
30 Proximal gastric vagotomy	$2x10^2$
33 Truncal vagotomy and pyloroplasty	$7x10^1$
22 Truncal vagotomy and antrectomy	$6x10^6$
14 Billroth I partial gastrectomy	$3x10^5$
24 Billroth II partial gastrectomy	$8x10^6$
45 2 Hours after cimetidine (1g/day)	$5x10^5$
42 10 Hours after cimetidine (1g/day)	$2x10^2$

Table 2. The frequency of isolation of bacteria (%) from hypochlorhydric patients (Author's series).

Organism	Intact (a) n = 65	Resected (b) n = 58	Carcinoma (c) n = 33
Escherichia coli	4.6	43.1	51.5
Clostridium sp.	1.5	6.9	24.2
Bacteroides fragilis	20.0	27.6	36.4
Micrococcus sp.	52.3	39.7	39.4
Streptococcus viridans	73.8	74.1	60.6
Streptococcus faecalis	84.6	86.2	72.7
Staphylococcus aureus	27.7	20.7	39.4

(a) with intact stomachs, (b) after gastric resection, and (c) with carcinoma.

c) Bile

The bile is normally sterile. The incidence of infected bile in patients with gallstones varies between 10 % and 20 % depending on age and the presence of common bile duct pathology. The incidence of infection in bile is over 80 % if there are stones or strictures in the common bile duct but is much lower in patients with malignant obstruction of the bile duct being approximately 30 % (Table 3). The most common bacteria isolated from infected bile are *Escherichia coli, Klebsiella spp.* and a variety of streptococci. Faecal anaerobes are extremely uncommon in bile, except in patients with bile duct strictures and after a previous by-pass procedure (Table 4).

Table 3. Incidence of bacteria in the bile (Author's series).

		n	% positive bile cultures
Acute cholecystitis (emergency operation)		29	82
Resolving acute cholecystitis		41	48
Mucocoele of the gall bladder		17	29
Empyema of the gall bladder		14	34
Normal gall bladder with stones	< 50 years	42	11
	50-70 years	37	13
	> 70 years	42	17
Stones in common bile duct		70	84
Stricture of the bile duct		8	100
Tumours of the distal bile duct		31	34
High bile duct obstruction from malignancy		8	50

Table 4. Bacteria in the bile (Author's series).

	Malignant obstruction	Cholelithiasis	Stricture	Previous bypass
AEROBIC				
Gram positive:				
Streptococcus faecalis	4 (9%)	30 (15%)	3 (8%)	5 (15%)
Beta-haemolytic streptococci	1	4	2	2
Streptococcus viridans	2	1	1	2
Staphylococcus aureus	3	3	0	0
Staphylococcus albus	1	4	0	3
Gram negative:				
Escherichia coli	10 (23%)	77 (38%)	12 (31%)	7 (21%)
Klebsiella aerogenes	7 (16%)	22 (11%)	2 (5%)	2 (6%)
Enterobacter spp.	3	8	1	0
Proteus spp.	2	13	3	1
Pseudomonas aeruginosa	2	4	2	1
Acinetobacter spp.	1	4	0	0
Serratia spp.	0	2	0	0
Aeromonas spp.	0	2	0	0
ANAEROBIC				
Gram positive:				
Clostridium welchii	4 (9%)	16 (8%)	3 (8%)	3 (9%)
Anaerobic streptococci	2	7		2
Gram negative:				
Bacteroides spp.	0	2 (1%)	7 (18%)	5 (15%)
Total	43	199	36	33

d) Small bowel

Counts of bacteria in the small bowel are usually less than 10^3 organisms per ml, but the counts increase in the terminal ileum. Counts exceeding 10^6 organisms per ml occur in patients with intestinal blind loops, Crohn's disease, and acute obstruction to the small intestine.

e) Colon

The colon always contains 10^{10}-10^{12} organisms per gram of faeces and the faecal anaerobes exceed the aerobic coliform bacteria by a factor of between 10,000 and 100,000. The principle pathogens in the colon are *Bacteroides fragilis, Clostridium sp,* anaerobic streptococci, *Escherichia coli, Proteus spp.,* and *Pseudomonas aeruginosa.* The influence of mechanical bowel preparation and oral antimicrobials on the faecal flora is shown on table 5. Mechanical bowel preparation alone had virtually no influence on colonic microflora apart from a modest reduction in counts of *E.coli* with elemental diets. Although oral metronidazole with neomycin had a profound inhibitory effect on colonic flora there was no reduction when metronidazole was used alone.

Tablo 5. Influence of bowel preparation on colonic microflora (Author's series) (log_{10} counts).

	No preparation	Mechanical prep Mag. sulphate	Elemental diet	Whole bowel irrigation	Oral antimicrobials	
					Metronidazole +Neomycin	Metronidazole alone
Staphylococci	$4x10^1$	$5x10^1$	$5x10^1$	$5x10^1$	$8x10^1$	5
Streptococci	$1x10^6$	$1x10^3$	$2x10^2$	$5x10^5$	$8x10^2$	$1x10^3$
Coliforms	$5x10^7$	$7x10^8$	$7x10^5$	$5x10^7$	$4x10^2$	$5x10^7$
Bacteroides	$2x10^8$	$4x10^8$	$9x10^6$	$2x10^8$	5	$9x10^7$
Bifidobacteria	$4x10^2$	$7x10^1$	$7x10^1$	$3x10^2$	5	$4x10^3$
Peptostresptococci	$2x10^3$	$1x10^1$	$3x10^1$	$6x10^1$	5	$2x10^1$
Clostridia	$8x10^3$	$2x10^1$	$6x10^1$	$1x10^3$	5	$4x10^2$

CHOICE OF PATIENTS SUITABLE FOR ANTIMICROBIAL PROPHYLAXIS

a) When not to use antibiotics

(i) Clean operations

There is no justification for using antibiotic prophylaxis during clean and uncontaminated operations. Clean operations may be defined as those in which the gastrointestinal, respiratory or urinary tract is not entered and in which there is not acute inflammation. Such intestinal procedures include proximal gastric vagotomy, rectopexy and postanal repair.

(ii) Respiratory sepsis

There is no evidence from the available literature that prophylactic antibiotics prevent chest infection unless the patient has established infective respiratory disease pre-operatively, in which case all elective operations should be cancelled. Vigorous physiotherapy and adequate analgesia should suffice for elective surgical operations.

b) Selective antibiotic prophylaxis advisable

(i) Gastro-oesophageal surgery

In elective gastro-oesophageal surgery endogenous sepsis is common following operations for gastro-oesophageal carcinoma, gastric ulcer, reconstructions for bile vomiting and emergency operation for gastrointestinal haemorrhage. However, infection is uncommon in patients requiring an operation for duodenal ulcer. Bacterial colonisation of the stomach is dependent upon the pH so that a policy of selective antimicrobial prophylaxis could be based upon the pH of gastric aspirates, however, in practice this policy has not been very successful. We would advise single dose antibiotic cover to all patients requiring operation for gastric ulcer, gastric or oesophageal cancer, revisional operations on the stomach, patients receiving cimetidine during operations, and for all patients requiring emergency surgery for gastrointestinal bleeding.

(ii) Biliary surgery

Sepsis in elective biliary surgery occurs most frequently following operations for common bile duct stones or strictures. In our institution we use a policy of selective prophylactic antibiotic cover which is restricted to the following groups of high risk subjects: patients over 70 years, jaundiced patients, subjects known to have choledocholithiasis and patients who have had a previous biliary operation.

c) Antibiotic prophylaxis for all cases

(i) Appendicectomy

Approximately a third of patients requiring an appendicectomy have established infection in the abdomen before operation, either because the appendix has perforated or become gangrenous, hence the term prophylaxis is inappropriate. Even the patients with acute appendicitis have a 6-16 % incidence of sepsis. The risk of sepsis even following interval appendicectomy or removal of a normal appendix is sufficiently high to justify the administration of single dose antibiotic to all patients, particularly when appendicectomy is performed in conjunction with biliary or gynaecological procedures.

(ii) Colorectal operations

The greatest risk of endogenous abdominal sepsis is amongst patients having elective colorectal operations. On account of the high incidence of infection of over 50% without antibiotic cover in patients with inflammatory bowel disease and colorectal carcinoma, prophylaxis by systemic antibiotics is advised for all patients. Like most colorectal surgery, I am convinced of the importance of a well prepared bowel and the use of peroperative rectal washouts, particularly now that the circular stapling devices are being used so widely for restorative rectal surgery. Faecal contamination when the bowel has to be opened during a low anterior resection not only increases the risk of sepsis but also of anastomotic dehiscence. Hence, antibiotics in colorectal operations will only be effective if the bowel preparation is adequate. If despite these measures there is extensive faecal contamination, or an abscess is encounted at operation, wounds should be left open, anastomoses avoided or protected and antibiotic administration prolonged for at least 5 days. The choice of antibiotics in colorectal operations should be by a combination of non-toxic systemic antibiotics effective against the principle aerobic and anaerobic pathogens in the colon.

CHOICE OF ANTIMICROBIAL AGENTS

a) Gastro-oesophageal surgery.

Ideally, the potential pathogens in the stomach should be identified and the antimicrobial agent chosen accordingly. Unfortunately, many different species may be pesent in the hypochlorhydric stomach and 2 or more agents might be required to provide cover against all of them. Moreover, the gastric microflora can change rapidly and so identification of the various species is not a practicable proposition.

The majority of studies on prophylactic antibiotics have included operations on several different sites, such as stomach, biliary system, appendix, and colon, in which the endogenous microflora is both qualitatively and quantitatively different. In each trial, the number of gastric procedures has been relatively small and the gastric pathology has not usually been stated. Thus, precise conclusions about the best choice of agent for use in gastric surgery cannot readily be drawn.

Systemic cephaloridine and cefazolin have both been successfully used (14,23) and are likely to be active against most of the common pathogenic gastric micro-organisms. The addition of metronidazole to extend the cover against anaerobic bacteria has been suggested (18) and this would certainly be advised for patients undergoing resections for gastro-oesophageal cancer particularly in view of the frequent location of *B.fragilis* in high concentrations from the stomach preoperatively.

Topical instillation of antibiotic solutions into the wound after peritoneal closure may be effective in reducing the incidence of wound infection (21,42), presumably because high concentrations can be achieved in the local tissues. However, serum levels of the antibiotic are inevitably low at the time of contamination and hence there is little, if any, protection against intra-peritoneal abscesses and septicaemia which are the really important causes of

mortality and serious morbidity. We conducted a prospective controlled trial to compare systemic with intraincisional cefuroxime for prophylaxis in patients requiring gastric resections (Table 6). The results indicate that systemic antibiotic cover with a single dose of intravenous antibiotic was safer than the use of the same agent into the wound at the end of the operation. For this reason, systemic antibiotic administration is to be preferred.

Tablo 6. Cefuroxime in gastro-oesophageal resection (Author's series).

	Systemic	Intraincisional	None
Wound sepsis	7%	4%	36%
Abscess	0	19%	29%
Septicaemia	0	4%	21%

Twenty years ago, Burke demonstrated experimentally the importance of giving an antibiotic before the incision is made. More recently it was found that while cefazolin administered 1-12 hours pre-operatively significantly reduced the incidence of infection, no benefit was obtained if the antibiotic was not started until 1-4 hours post operatively.

As a result of our own observations we now give all high risk patients (gastric cancer, gastric ulcer, previous gastric surgery, bleeding and patients needing H^2 antagonists during operation) a single dose of a cephalosporin immediately before the operation but we always add metronidazole in patients with gastro-oesophageal malignancy.

b) Biliary surgery

Four groups of antimicrobials are potentially useful in biliary surgery: penicillins, cephalosporins, aminoglycosides and the sulphonamides. Most of the early penicillins had a narrow spectrum of activity, and with the exceptions of flucloxacillin were unstable to β-lactamase. The newer agents such as mecillinam, piperacillin and ticarcillin are active against most of the aerobic Gram negative organisms likely to be encountered in bile, but they are not suitable for all coagulase positive staphylococci. The earlier cephalosporins such as cephaloridine or cephazolin have a wide range of activity and most aerobic biliary pathogens are sensitive, including staphylococci. The newer third generation cephalopsorins such as cefuroxime, cephamandole, cephotaxime and moxalactam are very active against Gram negative aerobes but are less active against staphylococci. The aminoglycosides such as gentamicin, tobramycin and amikacin are no longer recommended for prophylaxis, and should be reserved for life-threatening aerobic Gram negative infections since they are nephrotoxic unless carefully monitored. Furthermore, they have no activity against anaerobes. The sulphonamides have been popular in Scandinavia and their combination with trimethoprim in compounds like cotrimoxazole provide a useful safe agent for prophylaxis in routine elective operation (35).

There are certain important pharmacokinetic properties to take into consideration. Advantageous properties include low protein binding, long half-life, rapid bactericidal activity and good tissue penetration. It is also desirable, particularly in patients with cholangitis or those undergoing an operation, to have therapeutic levels of antibiotic in the bile, both to eliminate bacteria from the bile and to minimise postoperative sepsis. However, the majority of patients with infected bile have obstructive biliary disease and in these patients it is unlikely that adequate biliary levels of antibiotic can be achieved (30).

We believe that antibiotics which achieve satisfactory serum levels are more reliable to patients with obstructive biliary disease, than those which are excreted almost entirely into the bile. For most clinical situations it is desirable to use an antibiotic which provides both a high serum as well as high bile levels. Cephazolin is a good example of such an agent and one in which clinical trials have confirmed its efficacy (45). We would only advise the use of

metronidazole as well as cephazolin in patients with benign strictures of the bile duct.

c) Colorectal surgery

Operations on the colon and rectum are associated with a high incidence of post-operative sepsis unless some form of appropriate antimicrobial is used for prophylaxis (26,31). Infections after operations on the large intestine either occur at the time of the surgical procedure (primary sepsis) or in the post-operative period due to anastomotic dehiscence (secondary sepsis). Primary sepsis is usually due to organisms introduced from the lumen of the colon into the surgical field at the time of operation. Such microscopic bacterial contamination is almost inevitable during colorectal operations and may be responsible for wound infection, abscess or septicaemia. Primary sepsis should be preventable by appropriate antimicrobial prophylaxis. Secondary sepsis is usually due to problems of surgical technique and it is unlikely that antimicrobial prophylaxis will prevent these complications unless a perianastomotic abscess causes a subsequent anastomotic breakdown (17).

(i) Incidence of infection

There is a wide range in the reported incidence of infection in colorectal surgery. Factors which influence the rates of infection in elective operation include: the age of patients, the incidence of established infection such as abscess, fistulae or localised perforation, the type of surgical resection (anterior resection and abdomino-perineal excision having a much higher incidence of sepsis than right hemicolectomy) and the presence of a stoma. The rate of sepsis is naturally much higher when emergency operations are performed, particularly for perforation of the colon, large bowel obstruction and acute colitis. The duration of follow-up is also important since 40 % of wound infections occur after the patient has been discharged from hospital.

The incidence of sepsis in our unit before the use of antibiotic prophylaxis is illustrated in Table 7, the rate varying between resection for inflammatory bowel disease and cancer, and between emergency and elective operation. However, the results do not differ greatly from those reported by other groups, where the incidence of wound sepsis has varied from 35-50 %, abscess from 4-11 % and septicaemia from 4-35 % (4,6,8,19,29,46).

Table 7. Incidence of sepsis in colorectal surgery*,**

	Cancer		Inflammatory bowel disease	
	Elective operation n:83	Emergency operation n:29	Elective operation n:64	Emergency operation n:20
Wound sepsis (abdominal)	40%	60%	37%	42%
Perineal infections	79%	–	69%	–
Abscess	5%	13%	12%	22%
Septicaemia	10%	12%	7%	8%

*: Data from General Hospital, Birmingham., N.B. No of proctotomy's performed as emergency operations

**: No antibiotic cover

(ii) Organisms responsible

The bacteria isolated from clinical infections after colorectal operations are influenced by the care taken in isolating the strict anaerobes. For successful recovery of these organisms, specimens of pus must be taken directly to the microbiology department and if any delay is anticipated it is preferable to use a transport medium (such as Roberton's cooked meat broth). Leigh (32) showed that recovery of the strict non-sporing anaerobes from infections after bowel surgery increased four fold with the introduction of anaerobic techniques for culture. The bacteria isolated from patients on our unit having colorectal operations when no antibiotic cover was used are listed on Table 8. It can be seen that *Bacteroides fragilis* was the predominant organism. For some years there has been considerable debate as to whether both aerobic and anaerobic bacteria are primarily involved in the pathogenesis of post operative sepsis. Animal studies have suggested that the anaerobes are more important in the pathogenesis of abscess but that coliforms are the principal cause of septicaemia (39). In vitro studies, however, have clearly shown that there is synergy between *Bacteroides fragilis* and *Escherichia coli* (28). Quite low bacterial counts of *Escherichia coli* which would not normally be clinically important will cause postoperative sepsis if anaerobes are present. Similarly, if anaerobes are eliminated from a mixed bacterial inoculum by a specific anaerobicide, like metronidazole, the aerobic bacteria do not proliferate (24). Clinical data also supports the view that elimination of the anaerobic bacteria alone reduces postoperative sepsis and that no further reduction is achieved by addition of an antibiotic which is effective against *Escherichia coli.* There is substantial evidence that metronidazole, or lincomycin used alone significantly reduces both the aerobic and anaerobic infections in colorectal surgery, even though both agents have no activity against Gram negative aerobes (12,15).

Table 8. Bacterial isolates from sepsis after colorectal operations.*

Aerobes	
Staphylococcus aureus	7
Staphylococcus albus	15
Streptococcus faecalis	6
Beta-haemolytic streptococcus	6
Streptococcus viridans	7
Non-haemolytic streptococcus	7
Escherichia coli	46
Proteus sp.	10
Klebsiella aerogenes	8
Pseudomonas aeruginosa	9
Anaerobes	
Anaerobic streptococci	12
Clostridium sp.	13
Bacteroides fragilis	56

*: Data from General Hospital, Birmingham., No antibiotic cover.

(iii) Mechanical bowel preparation

Most surgeons consider that mechanical preparation of the colon by reducing the amount of faecal residue will reduce the risk of sepsis. There is no doubt that anastomotic dehiscence is more common if the bowel has been inadequately prepared before operation. However, we and others have shown that the efficiency of mechanical bowel preparation has no influence at all on the counts of bacteria in the colon. Hence mechanical preparation alone has no influence on faecal microflora.

Only two regimes have been shown to reduce the microflora of the colon: the combina-

tion of neomycin and erythromycin given on the day before operation results in a rapid reduction in most of the common aerobes and anaerobes in the colon (38). The combination of neomycin with metronidazole is even more effective at reducing the counts of *Bacteroides fragilis* than erythromycin and neomycin. Unfortunately prolonged exposure to neomycin results in an increasing incidence of neomycin resistant *Escherichia coli.*

(iv) Antimicrobial prophylaxis: general considerations

Prophylactic antimicrobials may be used by a variety of routes in elective colorectal surgery. Traditionally antibiotics have been used by the oral route to reduce the faecal microflora of the colon. The rationale of such therapy is that if colonic contents are released from the bowel, the bacterial inoculum will be sufficiently reduced to minimise sepsis. The oral route is undoubtedly effective, but there may be undesirable consequences such as overgrowth by yeasts or staphylococci. Furthermore, the oral route is inappropriate in patients with acute large bowel obstruction and in other emergency conditions. The other methods of prophylaxis include topical application of antibiotics into wounds or the peritoneal cavity and the use of systemic antibiotic cover.

The concept of giving oral antimicrobials to reduce colonic microflora stems from the observation that succinyl-sulphathiazole decreased the counts of faecal coliforms (40). Phthlalylsulphathiazole was used as the principal method of bowel preparation until neomycin was introduced. However, neither agent was shown to reduce post-operative sepsis, and as neither had any influence on the faecal anaerobes the poor clinical results are not altogether surprising. Overgrowth by *Staphylococcus aureus* and bacterial resistance was also a complication of the oral regimes (33). By contrast clinical studies using the combination of neomycin with erythromycin in America showed that the incidence of post surgical sepsis was significantly reduced (8). On our unit we reported a dramatic effect on faecal flora using a combination of oral neomycin and metronidazole.

The disadvantage of oral antimicrobials as pre-operative prophylaxis is that the intestinal aerobic bacteria rapidly become resistant to the antibiotics. Many oral agents such as neomycin and erythromycin do not provide predictable serum concentrations and are therefore quite inappropriate in emergency colorectal operations for obstruction or perforation of the colon.

(v) Systemic antimicrobial prophylaxis

Willis and others (47) reported that 5 days exposure to systemic metronidazole with a single dose of gentamicin compared with placebo reduced the rate of infection from 63 % to 15 %. Another trial indicated that with only 3 doses of intravenous metronidazole, the rate of sepsis was reduced from 51 % to 14 % even though there was a very high incidence of anastomotic dehiscence (16). Most trials of systemic antibiotic prophylaxis reported from the United States have used a cephalosporin (cephazolin or cephalothin) (9) in combination with the oral neomycin and erythromycin bowel preparation. However, the active agent in both studies appears to have been the oral antimicrobial bowel preparation and the addition of the cephalosporin did not seem to further protect against post-operative infection. There can be no doubt that prophylaxis directed entirely against the anaerobic pathogens has substantially reduced the risk of sepsis in colorectal surgery. The duration of systemic antimicrobial prophylaxis has also been questioned but the results of a recent controlled trial have shown that a single dose of metronidazole with cotrimoxazole given in the anaesthic room immediately prior to operation resulted in a sepsis rate of only 7 %. There was no difference in post-operative sepsis when the single dose regime was compared with prolonging the same antibiotic cover for 5 days (23).

(vi) Studies from author's experience

The results of clinical trials which span a period of 12 years are summarised in table 9. In 1972 we became aware of the importance of anaerobes as a cause of severe sepsis following operations for colorectal disorders. At that time, the only systemic antimicrobial available which was considered safe and effective against the obligate anaerobes was lincomycin. We therefore conducted a placebo controlled trial to investigate whether 5 day cover with lincomycin would reduce post-oerative sepsis. The findings of this trial which are reported in detail elsewhere confirmed the efficacy of 5 day cover with lincomycin, sepsis being reduced from 38% to 12%. In view of these findings we did not feel that it was ethical to proceed

with another control group. A subsequent study indicated that the addition of tobramycin to lincomycin did not improve upon the results of using lincomycin alone (sepsis 13 % and 12 % respectively). We therefore decided to study a further group of patients receiving lincomycin alone for only 24 hours (3 doses) in an attempt to determine whether short term antimicrobial cover was as good as conventional 5 day course of the same antibiotic. Somewhat to our surprise we found that 3 doses of lincomycin was almost as good as5 day cover (sepsis: 16 % and 12 % respectively). Unfortunately we felt obliged to discontinue our studies on the use of lincomycin because of a number of severe cases of pseudomembranous colitis which followed the use of this agent.

In early 1975 when intravenous metronidazole was not available, we decided that some other approach to the prevention of sepsis in colorectal surgery was called for. Studies in volunteers and patients requiring elective colorectal operations had shown that oral neomycin and metronidazole reduced the colonic faecal microflora. We therefore embarked upon a further prospective placebo controlled trial of oral erythromycin and metronidazole for elective colorectal surgery. In this study we reported a highly significant reduction in post-operative sepsis with the use of neomycin and metronidazole for 48 hours before operation and sepsis was reduced from 42 % to 17 % (34). Not only was wound sepsis reduced but there

Tablo 9. Clinical trials of prophylactic antimicrobial agents in elective colorectal resection (Author's series).

Trials no.	Agent	Year (and bowel prep.)	R/S	Route	Duration	n	% Wound	% Abscess	% Septic.	Other complications
1	Lincomycin	1973	R	IM	5 days	31	12	3	3	PMCx3
	Controls	(Mag.S.)				29	38	10	10	
2	Lincomycin + Tobramycin	1974 (Mag.S.)	S	IM	5 days	30	13	3	3	PMCx3
3	Lincomycin	1974 (Mag.S.)	S	IM	3 days	31	16	3	3	PMCx5
4.	Metronidazole + Neomycin	1975/6 (WBI)	R	0	2 days	51	17	0	0	
	Controls					59	42	5	12	
5	Metronidazole + Kanamycin	1977/78 (WBI)	R	IV/IM	3 doses	46	6	2	0	PMCx1
	Metronidazole + Kanamycin			0	3 days	47	36	2	4	PMCx6 Resistance
6	Metronidazole + Gentamicin	1979 Mannitol	R	IV/IM	2 doses	35	26	3	0	
	Cefoxitin			IV	2 doses	37	24	3	3	PMCx5
7	Metronidazole + Gentamicin	1980/81 Mannitol or (WBI)	R	IV/IM	2 doses	31	23	3	0	
	Metronidazole			IV	2 doses	29	17	0	0	
8	Metronidazole + Mezlocillin	1982/83 (Picolax)	R	IV	2 doses	49	30	6	2	
	Metronidazole + Cefuroxime	1983/84		IV	2 doses	47	24	0	2	
9.	Metronidazole + Latamoxef	1983/84 (Picolax)	R	IV	2 doses	56	23			bleedingx8
	Latamoxef			IV	2 doses	53	21	0	0	bledingx9
10	Metronidazole + Ceftriaxone	1984/85 (Picolax)	R	IV	1 dose	59	8	6	0	
	Metronidazole + Gentamicin			IV	1 dose	61	23	6	0	

PMC = Pseudomembranous colitis.
High infection rates wound sepsis>20%, Abscess or Septicaemia>10%. Bowel preparation: Mag.S.+Magnesium sulphate, WBI = whole bowel irrigation, Mannitol = oral mannitol. R=Randomised, S=Sequential.

were no intra-abdominal infections and no episodes of septicaemia with the active agents. Unfortunately after completion of this trial, we noticed that there was a high incidence of aerobic infections with oral neomycin and metronidazole. Furthermore, an audit of our infections indicated that between the years 1975 to 1977 there had been a threefold increase in the incidence of neomycin resistant *Escherichia coli* (11 % to 34 %).

In 1977 we designed a study to compare metronidazole and kanamycin used either orally or by systemic administration (27). The aim of oral therapy was to reduce the faecal flora of the colon without providing therapeutic serum concentrations of the drugs. The aim of systemic therapy was to provide high serum levels without influencing the colonic faecal microflora. To achieve these aims, the oral regime consisted of 1 g 8-hourly of kanamycin for 3 days and 400 mg 8-hourly of metronidazole for 2 days omitting the 3 metronidazole doses immediately prior to operation so as to avoid therapeutic serum levels. The systemic regime consisted of 3 doses of metronidazole (500 mg) and kanamycin (1 g). The first dose was given in the anaesthetic room, the second on the evening of operation and the last on the morning after operation. The oral regime failed to provide therapeutic serum levels of either metronidazole (0.4±0.6 mg/100 ml) or kanamycin (1.2±2.3 mg/100 ml). Systemic prophylaxis, however, achieved high serum levels of both metronidazole (13.2±5.7 mg/100 ml) and kanamycin (48.8±45.8 mg/100 ml). The oral regime was associated with a significant reduction in the bacterial counts of *Escherichia coli* from 10^7 to 10^3 and of *Bacteroides fragilis* from 10^7 to 10^2. On the other hand, systemic prophylaxis had no influence on the faecal flora. Abdominal wound sepsis occurred in 32 % of the orally prepared patients compared with 6 % in those receiving systemic prophylaxis. Antibiotic associated pseudomembranous colitis was recorded in 7 patients in the trial and six were in the patients who received oral antimicrobial bowel preparation. The reason for the high incidence of sepsis in patients prepared by the oral antimicrobials was a high incidence of kanamycin resistant *Escherichia coli* and *Staphylococcus aureus.* There were no metronidazole resistant anaerobic bacteria. In both groups of patients anaerobic sepsis was uncommon and the predominant cause of sepsis in the oral group was kanamycin resistant aerobes. The results of this study leave us in no doubt that oral antimicrobials used in an attempt to sterilise the colon prior to operation are potentially dangerous. Such a regime is associated with emergence of resistant organisms and any preparation which alters the normal intestinal flora will encourage development of pseudomembranous colitis and overgrowth of yeasts. Furthermore, oral agents are less effective at reducing post-operative sepsis than systemic antibiotic prophylaxis.

We felt that there might be advantages in using a single agent for systemic antimicrobial prophylaxis in colorectal surgery (20).

Cefoxitin, an agent with in vitro activity against most aerobic Gram positive and Gram negative bacteria and with great promise as an agent capable of irradicating *Bacteroides fragilis,* was therefore compared with metronidazole and gentamicin in a prospective trial which began in 1979. Unfortunately we reported a high incidence of post-operative sepsis in both groups. Furthermore, there were 6 serious infections from *Bacteroides fragilis* in the cefoxitin group compared with none in the group receiving metronidazole and gentamicin. We also recorded 5 cases of pseudomembranous colitis, all of these occurring after cefoxitin. We have subsequently shown that intravenous cefoxitin together with almost all broad spectrum cephalosporins has a marked suppressive effect on faecal flora which encourages overgrowth of *Clostridium difficile* which is now known to be the cause of pseudomembranous colitis (3) (Table 10).

It occurred to us that we should decide once and for all whether the addition of an aminoglycoside conferred any advantage to the use of metronidazole alone for prophylaxis. This study was prompted by the excellent clinical results reported with metronidazole alone and the in vitro evidence that suppression of aerobes might allow the normal defence mechanisms to prevent the growth of aerobic bacteria. The results of this study (37) indicated that metronidazole alone was just as effective as three combination of metronidazole with gentamicin (sepsis : 17 % and 23 % respectively). However, the high rates of infection were somewhat disappointing.

Table 10. Influence of single dose IV antibiotics on faecal flora.

	n	C. difficile	Aerobes	Anaerobes
Benzylpenicillin	6	0	0	0
Ampicillin	6	0	0	0
Mezlocillin	6	0	0	0
Piperacillin	6	0	0	0
Ticarcillin	6	0	0	0
Cephaloridine	6	0	0	0
Cephazolin	6	1	0	0
Cefuroxime	6	1	0	0
Cefoxitin	6	2	0	$-1x\log_{10}$
Cefotaxime	6	2	$-1x\log_{10}$	0
Latamoxef	6	3	0	0
Ceftriaxone	6	2	$-2x\log_{10}$	$-2x\log_{10}$
Cefotetan	6	4	$-2x\log_{10}$	$-2x\log_{10}$

Metronidazole and cefuroxime were compared with metronidazole and mezlocillin (2). There was a high incidence of sepsis in both groups, cefuroxime being associated with pseudomonas infection in 7 cases and mezlocillin being associated with 9 staphylococcal sepsis. Neither regime seemed suitable for colorectal surgery.

Latamoxef is a broad spectrum cephalosporin with good in vitro activity against *Bacteroides fragilis*. We decided therefore to compare latamoxef alone with latamoxef and metronidazole in a prospective randomised trial (36). Infection rates in both groups were over 20 % but severe bleeding was recorded in 17 % of patients receiving latamoxef alone compared with 14 % in the group receiving latamoxef and metronidazole. Episodes of bleeding which often necessitated reoperation was associated with prolonged prothrombin times. This phenomenon has also been recorded with other third generation cephalosporins. Furthermore, there were 6 severe anaerobic infections in the latamoxef group compared with only 1 when latamoxef was combined with metronidazole. These results mirror our earlier findings with cefoxitin and suggest that in vitro the cephalosporins are not sufficiently active agains the obligate anaerobes to be relied upon.

Our most recent trial has compared a single dose of a long acting cephalosporin (ceftriaxone) with metronidazole (1.5g) against metronidazole and gentamicin (43). Ceftriaxone achieved a high serum concentration for 24 hours as did high dose metronidazole and was associated with a wound sepsis rate of only 7 %. This is one of the best results yet achieved on our unit and is we believe due to maintaining adequate serum levels for 24 hours.

(vii) Special considerations in complicated colorectal surgery

So far, we have considered only the use of antimicrobial agents for prevention of infection in colorectal surgery when there is no preoperative contamination. However, the situation is different if there is pre-existing infection from a fistula, perforation of the colon or a local abscess, as in many cases of inflammatory bowel disease. Under these circumstances it may be prudent to use antibiotics which will be bactericidal to both the aerobes and the anaerobes. Furthermore, in our experience it is sometimes unwise to use a mechanical bowel preparation as this may lead to serious septic complications together with the risk of perforation. Another category of patients with complicated colorectal pathology are those with large bowel obstruction, in whom bowel preparation is impossible. Also included in this high risk group are patients requiring operation who have an established stoma where contamination by intestinal bacteria is inevitable. It is surprising that more clinical trials have not been performed in patients requiring complicated colorectal surgery or for operations where there is established contamination. Two restrospective reports claimed that short term systemic

antimicrobial prophylaxis had no beneficial effect in such patients (1,22). Both studies reported, however, that the use of corticosteroids for inflammatory bowel disease was not associated with an increased risk of sepsis.

We have completed only two studies on the use of antimicrobials for patients requiring resection for inflammatory bowel disease. The initial study was to compare short term antimicrobial cover using 3 doses of metronidazole and gentamicin with placebo injection or infusion (Table 11). There was a small reduction in sepsis which was not statistically significant in the group receiving the active drugs compared with placebo (sepsis: 30 % and 44 % respectively). We subsequently undertook a separate study to compare 5 day cover using metronidazole and gentamicin with our previous results. The infection rate using prolonged antimicrobial cover was only 13 %. We would conclude therefore that for complicated colorectal operations in situations where there is established infection or contamination at the time of operation it is preferable to use prolonged antimicrobial cover. By contrast, short term antimicrobial cover seems to be adequate in elective operations where there is no gross contamination.

Table 11. Trial of systemic antibiotics for resection*-in inflammatory bowel diseases (Patients with perforation excluded).

		RANDOMISED TRIAL	SEQUENTIAL STUDY
	Controls	Metronidazole and Gentamicin IV 3 doses	Metronidazole and Gentamicin IV 5 days
Number	27	30	30
Abdominal wound sepsis	37%	23%	12%
Perineal sepsis	4/6	1/8	3/8
Abscess	11%	10%	3%
Septicaemia	7%	10%	–
Total number with sepsis	44%	30%	13%

* = Data from General Hospital, Birmingham.

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