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Indications for antibiotic prophylaxis and treatment in patients undergoing appendicectomy

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Bacteroides species were isolated from 225 (66%) of positive appendix fossa swabs examined from 830 patients undergoing appendicectomy and were the commonest organisms isolated in pure culture. Pathogenic bacteria were more frequently isolated from the appendix fossa swab in perforated appendicitis. The incidence of wound infection in 553 patients who did not receive antibiotic treatment was 22% and this was highest in perforated appendicitis (69%) and appendix abscess (94%) and lowest where chronic appendicitis (11%) was present. *Bacteroides* species were isolated from 89% of wound infections where a mixed culture was present and 82% when a single organism was found.

The role of antibiotic prophylaxis is important in reducing the rate of wound infection, especially in perforated appendicitis, but treatment should also be given when *Bacteroides fragilis* is isolated from the appendix fossa swab in view of the high incidence of wound infection in these cases. The use of clindamycin, lincomycin and metronidazole is considered more appropriate than other antibiotics because of their high level of antibacterial activity against anaerobic bacteria. It is important to detect 'patients at risk' in view of the dangers associated with widescale use of antibiotic prophylaxis. Despite many published reports, the morbidity associated with appendicectomy is high and further controlled studies involving the close co-operation of the surgeon and microbiologist are needed.

Introduction

Acute appendicitis is the commonest surgical emergency seen in a routine hospital. Although occurring most frequently in children and young adults, the age range is wide and this condition can occur with serious morbidity in the older age groups. The symptomatology is not always characteristic and many patients require surgery to make confident diagnosis. In the High Wycombe and Amersham group of hospitals, which serves a population of 250,000, between 470 and 500 operations are performed each year, giving a prevalence of 2 per 1000 population per year. Whilst many aspects of the surgical management of patients with appendicitis are clearly defined, there is still discussion about the value of wound drainage and primary wound closure, especially in patients with perforated appendicitis. The role of antibiotic prophylaxis in appendicectomy has been the subject of many reports, and various antibiotics and antiseptics have been shown to significantly reduce the incidence of wound infection. This paper presents bacteriological and therapeutic details of 830 patients undergoing appendicectomy in the High Wycombe and Amersham General Hospitals.

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Clinical, macroscopical and histological findings

The majority of the 830 patients presented with the typical clinical signs of acute appendicitis but of varying severity, and the operation was usually carried out as an emergency procedure. Patients with appendix abscesses discovered at surgery and those undergoing interval appendicectomy were also included, together with a few patients who had an appendicectomy carried out in addition to the primary surgical procedure. There were 443 women and 387 men with a wide age range of between 2 and 88 years. Two groups of 100 patients were part of a double blind trial comparing a single dose 600 mg lincomycin hydrochloride as prophylaxis in appendicectomy with control patients receiving saline (Leigh, Pease, Henderson, Simmons & Russ, 1976) and a further 124 patients were included in prospective studies of the use of systemic clindamycin phosphate in serious post operative infections (Leigh, Simmons & Williams, 1977*a*, 1977*b*). All appendices were examined macroscopically and histologically. An abnormality of the appendix was present in 739 (89%) patients. Four hundred and eight (49%) showed acute inflammation frequently with early gangrenous changes, 151 (18%) macroscopic or microscopic perforation, 32 (4%) abscess formation, 91 (11%) reactive lymphoid hyperplasia and 57 (7%) chronic appendicitis with an increase in fibrous tissue due to past inflammation. The remaining 91 (11%) appendices were considered to be normal.

Problems associated with appendicectomy

The incidence of post-operative infective complications following appendicectomy is high. The most important reasons for this are presence of peritoneal contamination following perforation of the appendix or accidental contamination during surgery. However, many appendicectomies are carried out by the most junior member of a surgical team, often during the night when the facilities of the Microbiology Laboratory may not be fully available or be inadequate due to inexperienced staff. There may also be a delay in starting the operation because of lack of theatre time and facilities. Whilst bacteriological examination is usually performed when frank pus is present at surgery, the routine swabbing of the appendix fossa in non-perforated appendicitis is not universally carried out. It has been reported (Leigh, Simmons & Norman, 1974) that the presence of pathogenic bacteria, particularly *Bacteroides fragilis*, in the appendix fossa at the time of operation has predictive value in the development of post-operative sepsis. Other workers (Longland, Gray, Lees & Garrett, 1971; Lari, Kirk & Howden, 1976) have reported similar findings in smaller studies and have also made the observation that a non-specific peritoneal swab is of considerably less value than one taken from the appendix surface or from the wound after removal of the appendix.

Prophylaxis and incidence of wound infection

The aim of prophylaxis is to provide a high concentration of an antibacterial agent in the wound at the time of greatest risk. The antibiotic can be prescribed before surgery when the diagnosis is established, or during the operation when the condition of the appendix or presence of perforation and abscess formation can be confirmed. Whilst parenteral therapy is probably necessary when prophylaxis is given pre-operatively, at surgery or in the immediate post-operative period, the antibiotic or an antiseptic can also be used topically in the form of a concentrated solution, powder or aerosol spray. When bacteriological examination of the appendix fossa is carried out, it is possible to prescribe an antibiotic when the results of culture are known as an interim report can be issued after 12 to 18 h by the laboratory that uses selective anaerobic media.

The incidence of wound infection varies considerably with individual studies and a rate of between 10% and 33% has been reported in untreated patients. However, the severity of the appendicular disease plays a paramount role in the incidence and this rises to between 50% and 80% (Gurry, King, Rutter & Brooke, 1976; Clark, 1976) when the appendix has perforated. In the present study, 553 of the 830 patients did not receive antibiotics and the incidence of post-operative wound infection is shown in Table I. Whilst the overall incidence was 22%, in perforated appendicitis this rose to 69%. In operations where the appendix was normal, the incidence of wound infection (18%) was higher than in all other non-perforated groups. Wound infections following appendicectomy where there is no macroscopic or histological abnormality are surprisingly common, the incidence frequently being higher than when acute inflammation is present. The only explanation for this finding is a failure of surgical technique with peritoneal and wound contamination. The lowest incidence of infection (11%) was seen when there was chronic appendicitis with a fibrotic appendix.

Table I. Incidence of wound infection compared with histological findings in appendix

Histological finding	Total	Wound infection
Normal	71	13 (18%)
Lymphoid hyperplasia	73	9 (12%)
Chronic	46	5 (11%)
Acute	288	40 (14%)
Perforated	59	41 (69%)
Abscess	16	15 (94%)
Overall total	553	123 (22%)

Bacteriological examination of the appendix fossa

A swab was taken from the appendix fossa before disturbing the appendix and placed in Robertson's meat broth. In the laboratory the swab was cultured onto blood, MacConkey and a selective agar for yeast isolation, and blood and neomycin blood agar (0·1 g/l) incubated anaerobically. Subculture was carried out from the Robertson's meat broth onto a similar set of agar plates. Bacterial isolates were speciated by routine laboratory methods. The majority of *Bacteroides* strains were subspecies *fragilis* but not all were fully identified.

The bacteriological findings in 830 appendix fossa swabs are shown in Table II. Pathogenic bacteria were isolated from 387 (47%) of the swabs and a pure growth was found in 155 (40%) cases. The commonest bacteria grown were *Bacteroides* species (66%) and *E. coli* (49%) but other Gram-negative bacilli, apart from *Klebsiella/Enterobacter* species (18%), were rarely isolated. Gram-positive organisms were isolated less frequently, the commonest being *Streptococcus faecalis* [present in 44 (11%)

Table II. Bacteriological findings in 830 appendix fossa swabs

Pathogenic bacteria isolated	387 (47%)	
Mixed aerobic and anaerobic growth	232 (60%)	
Pure growth	155 (40%)	
Bacteria isolated	**Total isolates**	**Pure growth**
Bacteroides species	255 (66%)	54 (35%)
E. coli	188 (49%)	49 (32%)
Klebsiella/Enterobacter species	69 (18%)	14 (9%)
Pseudomonas aeruginosa	18 (5%)	3 (2%)
Proteus species	9 (3%)	—
Strep. faecalis	44 (11%)	7 (4%)
Streptococcus species*	42 (11%)	15 (10%)
Clostridium welchii	33 (9%)	—
Anaerobic streptococci	25 (6%)	6 (4%)
Staph. aureus	11 (3%)	7 (4%)

* Include α, β and non-haemolytic strains.

swabs] but other species of streptococci including α, β and non-haemolytic strains were isolated from 42 swabs. When a pure growth of a single bacterial strain was present, *Bacteroides* species were found in 35% of swabs and *E. coli* in 32%. Strains of streptococci other than *Strept. faecalis* and anaerobic streptococci were found as commonly as in mixed culture.

Although *Staphylococcus aureus* was isolated from only 11 swabs, in 7 (64%) this species was present as the single pathogen, and the aetiology of this organism in appendicitis is difficult to assess. There was no significant increase with the other bacterial species isolated. As expected, the isolation of pathogenic bacteria was significantly greater when perforation of the appendix was present (Table III) than in other categories, and this was particularly striking with species of streptocci.

Wound infection

Wound infections developed in 123 of the 553 untreated patients in the study, but bacteriological examination was carried out in only 85 patients and in 11 no bacterial

Table III. Relation between bacterial isolation and histological findings

Histological findings	Total	*Bacteroides* species	*E. coli*	*Klebsiella/Enterobacter*	*Strep. faecalis*	*Strep.* species	Anaerobic strep.
Normal	37	24	20	1	7	1	2
Lymphoid-hyperplasia	46	33	20	8	8	1	2
Chronic	30	21	7	9	2	4	—
Acute	36	21	15	8	4	3	2
Perforated	79	58	47	13	7	13	7
Abscess	94	69	47	13	6	19	13

Table IV. Bacteriological findings in 74 wound infections

	Total	Mixed culture	Pure culture
Total No.	74	36	38
Bacteroides species	63 (85%)	32 (89%)	31 (82%)
E. coli	20 (27%)	15 (42%)	5 (13%)
Klebsiella/Enterobacter	9 (12%)	8 (22%)	1 (3%)
Pseudomonas aeruginosa	4 (5%)	4 (11%)	—
Proteus species	3 (4%)	2 (6%)	1 (3%)
Strep. faecalis	6 (8%)	6 (17%)	—
Streptoccus species*	7 (9%)	7 (19%)	—
Anaerobic streptocci	3 (4%)	3 (8%)	—
Clostridium welchii	2 (3%)	2 (6%)	—
Staph. aureus	5 (7%)	5 (14%)	—

* Includes α, β and non-haemolytic strains.

growth was found. The findings are shown in Table IV. *Bacteroides* species were isolated in 63 (85%) of the positive swabs and the incidence was the same in swabs with mixed or pure culture. *E. coli* was found in only 20 (27%) of positive swabs and, in common with other species isolated, was rarely seen as the single organism responsible for wound infection. Pathogenic bacteria were present in the appendix fossa swab in 55 (74%) of the 74 positive wound infections swabs, and there was little difference in the isolation rate between the various strains, suggesting that the wound infection flora closely paralleled the fossa flora. However, when the total number of isolations from the appendix fossa swabs in untreated patients was considered, *Bacteroides* species were twice as likely to cause an infection, especially when isolated on primary culture (Table V). When no growth was obtained from the appendix fossa swab, wound infection developed only 16 (5%) of 296 patients, but 12 of the infections were caused by *Bacteroides* species, usually in pure culture.

Table V. Incidence of wound infection related to initial bacteriological findings in appendix fossa swab (untreated patients only)

Initial finding	Total	Number infected with same organism
Bacteroides species 1° culture	63	25 (40%)
2° culture	85	20 (24%)
E. coli	79	15 (19%)
Klebsiella/Enterobacter	51	5 (10%)
Proteus species	5	1
Strep. faecalis	28	2 (7%)
Streptococcus species	16	2 (12%)
Anaerobic streptococci	12	2 (17%)
Staphiaureus	5	—
No growth	296	16 (5%) (*Bacteroides* species 12)

The isolation rate of pathogenic bacteria from appendix fossa swabs was relatively high in all histological groups except when the appendix was normal. As the incidence was considerably higher in the infected cases than in non-infected cases, it seems likely that the results of bacteriological examination are a useful indication of the likelihood of wound infection.

Antibiotic prophylaxis in appendicectomy

Many studies of the use of antibiotic prophylaxis in appendicectomy have been reported but there is still considerable disagreement as to the best compounds and route of administration. In the past, the results of most trials of parenteral antibiotics have been disappointing (Longland *et al.*, 1971; Magarey, Chant, Rickford & Magarey, 1971), with the possible exception of cephaloridine, where there are indications (Everson & Nash, 1976) that a 3 day course in patients with perforated appendicitis may result in a significant reduction in wound infection. Antibiotic solutions or powders such as ampicillin (Rickett & Jackson, 1969; Mountain & Seal, 1970), tetracycline (Benson, Brown & Whittaker, 1973) or cephaloridine (Evans, Pollock & Rosenberg, 1974) have been used locally, and success has been reported with povidone iodine (Gilmore, Martin & Fletcher, 1973). However, the use of other antiseptics such as noxythiolin (Bird, Bunch, Croft & Hoffmann, 1971; Gurry *et al.*, 1976) and chlorhexidine (Crosfill, Hall & London, 1969) did not reduce the incidence of infection. The difficulties associated with many of these studies are that no account was taken of the degree of infection present or the severity of the appendicular disease, and several different regimes have been used in any one study. As pointed out by Honigman & Rushton (1973) the poor results of Crosfill and his colleagues (1969) using chlorhexidine would be significantly altered by considering the state of the appendix, and Airan, Levine & Sicé (1973) recorded basic criticisms of the controlled trial of Gilmore *et al.* (1973) in which two factors had not been analysed.

As *Bacteroides fragilis* is the commonest organism isolated from wound infections following appendicectomy and is frequently found as the only organism, it is not surprising that parenteral antibiotics with low anti-bacterial activity against this species should show such disappointing results. The use of the same dose of antibiotic in the form of a local solution applied to the wound provides a very high local concentration of the antibiotic, which may be effective against the majority of strains of *Bacteroides fragilis*. It is rational, therefore, to try the use of a parenteral prophylactic antibiotic with a high degree of activity against anaerobic bacteria.

The use of lincomycin has been shown to be successful in reducing the incidence of wound infection after appendicectomy for non-perforated appendicitis from 17% in untreated controls to 6% (Leigh *et al.*, 1976). In an earlier retrospective study (Leigh *et al.*, 1974) which included perforated appendicitis, the incidence of wound infection followed a full course of lincomycin treatment, usually combined with ampicillin, was 15%, whereas if ampicillin alone or inappropriate antibiotic treatment was used the incidence was over 50%. More recently clindamycin therapy in severe, acute or perforated appendicitis was successful in preventing wound infection in 87% of patients (Leigh *et al.*, 1977*a*), thus confirming the results of Okubadejo (1976). Metronidazole, a chemotherapeutic substance with a consistent bactericidal activity against anaerobic bacteria, prevented post-operative anaerobic infection completely in a group of 49 patients undergoing appendicectomy (Study Group, 1976) and there is no doubt that this substance will be of great benefit both as a prophylactic and therapeutic agent.

The importance and role of antibiotic prophylaxis

The development of post-operative infective complications, especially wound infection, following all surgical procedures involves many factors. Some of these are directly related to the patient, the most important being the severity of the disease and the patient's general condition. Early diagnosis of the possibility of appendicitis by the general practitioner and hospital doctor will lead to rapid surgery which may prevent performation taking place. However, in the elderly with lowered defence and immune mechanisms, perforation of the appendix may not be accompanied by a crisis in their illness. In contrast, in the young patient the interval between acute inflammation and perforation may be short. The symptoms will also depend on the location of the appendix; the retrocaecal or pelvic position may produce relatively few characteristic clinical signs. Even after diagnosis rapid surgery may not be possible, as many hospitals suffer a chronic shortage of operating theatre time and the patient may have to wait several hours before surgery. In these circumstances, the services available to patients may be of a lower standard than usual, especially when the operation is carried out after normal working hours; this is of paramount importance when perforated appendicitis is present. Another factor related to the hospital is the availability of a bacteriology service able to carry out anaerobic culture, even out-of-hours.

The surgeon plays a significant role in the development of wound infection as appendicectomy is frequently an operation carried out by the most junior house surgeon and even though there may be adequate supervision, accidental peritoneal contamination may occur. Many cases which appear simple may prove to be technically difficult due to complications arising during the course of the operation. Surgical expertise and technique will limit the incidence of infective consequences. The availability of a reliable bacteriological service will increase the number of patients who have samples examined. Until recently, the main surgical indication for collecting specimens for bacteriological examination has been 'pus', but more emphasis is being laid on the routine collection of samples which may be valuable, not only in providing the identity and the antibiotic sensitivity of the infection organisms, but also in proving a sterile wound. The isolation of certain bacteria, particularly *Bacteroides fragilis,* predicts the likely development of wound infection, and although the effectiveness of delayed antibiotic prophylaxis is still the subject of discussion, there is no doubt that if given in the first 24 h after operation it will prevent or abort many infections.

The aim of antibiotic prophylaxis is to provide a high concentration of an effective antibacterial agent in the wound area during the operation and this can include all patients undergoing appendicectomy or only selected patients. The problems associated with the universal prescription of antibiotics are well known. It may be unnecessary in a large majority of patients where the surgery is uncomplicated but wound infections are relatively common in normal appendicectomies (Table I).

The dosage and timing of the treatment may be ineffective due to delay in surgery beyond the half-life of the antibiotic, and failure to recognise this possibility frequently results in low tissue concentrations during the operation. The development of resistant bacteria may be induced either by R-factor transfer or chromosomal change and the effect of antibiotics on the normal flora may select potentially pathogenic bacteria. The widespread use of any particular antibiotic will increase the prevalence of toxicity and may bring to light unrecognised side effects. The universal use of prophylaxis, therefore, is regarded as unscientific and it is essential to try to detect the group of patients who are at risk.

The presence of gross peritoneal contamination due to perforation of the appendix or surgical accident is a primary indication for antibiotic treatment. However, microscopic contamination of the peritoneum may occur and the detection of this necessitates both bacteriological and histological examination. In the past, many bacteriological services have been inadequate due to failure to isolate anaerobic bacteria. However, with improvements in specimen collection, transport and selective laboratory culture, many laboratories can now detect and identify anaerobic bacteria after 12 to 18 h incubation. When pus or purulent material is available, gas chromatography can also provide a more rapid diagnosis. There appears, therefore, little justification for not routinely screening all patients undergoing appendicectomy by collecting a swab from the appendix fossa.

A critical factor in the success of prophylaxis or treatment is the antibacterial agent used. The commonest organism isolated both from the appendix fossa and post operative wound infection is *Bacteroides fragilis,* which is not surprising, as this organism is the predominant species in the faeces. Its pathogenicity is undoubted as it is isolated from over 80% of wound infections after intestinal surgery (Leigh, 1974) and it is frequently present in pure culture. Further evidence which substantiates its pathogenicity is the higher incidence of wound infections in patients in whom this organism has been found on primary culture of the appendix swab. It is essential, therefore, than an antibiotic with effective activity against *Bacteroides fragilis* is used in prophylaxis. Antibiotics such as clindamycin, lincomycin and metronidazole have been shown to give adequate protection when given before or at the end of surgery. Although the use of other compounds such as the penicillins, cephalosporins and tetracycline may be effective as a local prophylaxis in the wound, it is doubtful whether it is justifiable to use these alone. Many studies have found that *E. coli* is frequently isolated, and when anaerobic techniques are inadequate it is the commonest organism. Its role in post-operative wound infections is difficult to assess, however, for when isolated in mixed culture with anaerobic and other aerobic bacteria, it has been shown that clindamycin alone is as effective as combination therapy (Leigh, 1973; Gorbach & Thadepalli, 1974). There is no doubt that *E. coli* can be a primary pathogen and it should not be disregarded in the therapeutic regime. Other organisms such as streptococci may be responsible for isolated wound infections and it is prudent that the treatment of perforated appendicitis includes antibiotics active against anaerobic and aerobic bacteria. Despite the large volume of published literature on the prevention of post-operative infective complications following appendicectomy, the incidence of wound infection is still too high to allow complacency and more controlled studies involving the close co-operation of the surgeon and bacteriologist are needed. Antibiotic prophylaxis, therefore, either limited to the period of the operation or as a full therapeutic course, is a vital part of the surgical care of the patient, and whilst there may be clinical reasons for its use, the isolation of certain bacteria from routinely collected appendix fossa swabs is a positive indication to prescribe antibiotics even in the early post-operative period.

The upsurge in interest in anaerobic bacteria has been described as yet another example of a 'band wagon' approach. However, evidence is being rapidly accumulated in many spheres of surgery other than the gastrointestinal tract that anaerobic bacteria are significant and important pathogens in post-operative infections, and that recognition of this, together with appropriate chemotherapy, provides a more successful outcome to surgery for the patient. However, the increased isolation rate of anaerobic bacteria from non-infected areas associated with improved specimen collection and laboratory culture lays a responsibility on interested workers to devise techniques for distinguishing between normal flora and true infections, and detecting the 'patients at risk'.

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