Clinical Importance of Infections due to *Bacteroides fragilis* and Role of Antibiotic Therapy

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Summary

Out of 200 infections due to *Bacteroides fragilis* occurring over a period of three years 133 were related to the intestinal tract, 55 to the genitourinary tract, and the remainder were in bedsores and ulcers; 56% occurred in patients undergoing major intestinal surgery.

B. fragilis was isolated in pure culture from 56% of the infections. In mixed culture it was most commonly associated with *Klebsiella* and *Enterobacter* species. Other anaerobic bacteria were isolated in 9% of the mixed cultures.

Altogether 131 (65.5%) of the patients recovered without antibiotic therapy or further surgery, but 59 (29.5%) developed complications and 10 (5%) died. The commonest complication was abscess formation, and the incidence was highest with infections associated with malignancy (44%) and lowest with obstetric infections (5%). The mortality was 5% overall but in the presence of bacteraemia it rose to 33%.

Only 43 patients received appropriate chemotherapy. Clindamycin was the most effective antibiotic, having a recovery rate of 78%, but this rate was little better than in untreated patients (65%). The role of prophylactic antibiotic therapy in preventing bacteroides infection remains to be studied.

The incidence of the isolation of bacteroides from wound infections after major intestinal surgery rose from 13% in 1970 to 81% in 1973. This increase was due to both the accurate collection and care of specimens while in transit to the laboratory and the use of selective media for the isolation of bacteroides in laboratory culture. The importance of these precautions is emphasized.

Introduction

The clinical importance of *Bacteroides* species in infection was first recognized by Vincent (1896), Hallé (1898), and Veillon and Zuber (1898), though Pasteur (1863) had previously reported the existence of bacteria surviving without oxygen and their role in putrefaction. Since then there have been numerous reports about the isolation of this group of anaerobic bacteria in various types of infection but the true incidence in post-operative infections is unknown.

Bacteroides constitute the major group of bacteria in the faeces and account for over 90% of the total bacterial population. It is likely, therefore, that the major source of infection would be the gastrointestinal tract, and Gillespie and Guy (1956) and Gunn (1956) reported that most infections occurred after intestinal surgery. Wilson *et al.* (1972) found that 73% of their patients with bacteraemia had underlying intestinal disease. In gynaecological and obstetric disorders *Bacteroides* has been reported as the most common pathogen

(Ledger, 1972) and the cause of serious post-partum infection (Pearson and Anderson, 1970). Severe infections occur in patients with carcinoma (Gelb and Seligman, 1970), especially in the older age group (Sinkovics and Smith, 1970; Ellner and Wasilauskas, 1971).

The difficulties in isolating anaerobic bacteria in a routine laboratory have been described by Stokes (1958), and recent improvements in cultural techniques and anaerobic incubation (Collee *et al.*, 1972) have led to more frequent isolation and a revived interest in this group of bacteria.

Over the past three years a wound infection survey has been carried out in the Wycombe group of hospitals and the number of isolations of bacteroides has greatly increased. This paper describes a group of 200 patients with significant bacteroides infections, reports the results of treatment and eventual outcome of the infection, and examines the antibiotic sensitivities of this group of anaerobic bacteria.

Patients and Methods

The majority of patients with bacteroides infections were hospital inpatients admitted for surgery. A few developed their infections after discharge from hospital and another group were diagnosed after minor surgical procedures carried out in the outpatients and accident departments.

Only patients with significant infections associated with fever, abscess formation, and delayed wound healing were included in the study. Details of the patients and treatment were abstracted from either the inpatients notes or the control of infection sister's wound infection survey charts. Recovery was defined when the infection subsided rapidly either with further surgery of chemotherapy or without specific therapy. Complications were deemed to be present when the initial infection led to severe local or metastatic abscess formation or the development of thrombophlebitis and jaundice.

Collection and Transport of Specimens.—The specimens were either sent to the laboratory by the clinician or requested by the control of infection sister as part of the postoperative wound infection survey. Most of the specimens were swabs taken from the wound infection but samples of pus were also received. In genital infections vaginal and intrauterine swabs were examined. In many cases the swab was obtained at the time of surgery. All swabs were delivered to the laboratory as quickly as possible and in the latter part of the study were sent in either Stuart's transport medium or Robertson's meat broth. Transport media were always used when there was likely to be an unavoidable delay in delivery to the laboratory.

Laboratory Investigation.—As soon as possible after being delivered to the laboratory the specimens were cultured by routine bacteriological methods, which included inoculation on to blood agar for aerobic and anaerobic incubation and on to MacConkey agar and in many cases subculture into Robertson's meat broth. In the latter part of the study a selective medium, blood agar containing 0.02% neomycin, haemin, and vitamin K, was also used. Anaerobic incubation was carried out in jars using the Gaspak system (B.B.L., Maryland, U.S.A.) immediately after inoculation and the plates were examined for at least 48 hours. After incubation the Robertson's meat broths were subcultured on to a similar set of agar plates. Identification of the strains of bacteroides was carried out by studying their cell morphology and biochemical reactions (Cowan and Steel,

1965). Accurate antibiotic sensitivities were determined for a large number of strains of bacteroides using a plate dilution method on blood agar. Nine chemotherapeutic substances were used. Inoculation of the agar was carried out using a phage-typing machine and the inoculum size was approximately 10^5 bacteria per ml or 10^8 bacteria per loop. The inhibitory concentration was the point at which there was no bacterial growth.

Results

During January 1970 to June 1973 bacteroides were isolated from significant infections in 200 patients, 123 of whom were female and 77 male. Their ages ranged from 9 to 90 years, the average being 40 years. The largest number of infections in women occurred between 20 and 40 years of age and in men between 60 and 90 years of age.

The number of isolations increased from 20 in 1970 to 41 in 1971, 61 in 1972, and 78 in the first six months of 1973. Altogether 137 of the patients had undergone major surgical procedures, in 114 cases to the gastrointestinal tract, and 21 had had minor surgical operations, mostly incision of abscesses (14); 42 patients, including some of those with bacteraemia, all of those with skin infections, and most of those with genitourinary infections, had not undergone surgery.

The infection was diagnosed from swabs taken at the time of surgery in 52 patients and from a subsequent wound infection in 110. In 17 out of 30 patients with genitourinary tract infections bacteroides were isolated from an intrauterine swab, the remainder being from vaginal swabs. Bacteroides were isolated from a blood culture in 15 patients and in eight this was the only source of these organisms.

The underlying diseases and surgical procedures associated with 149 of the infections are shown in table I. The largest number of infections were associated with the appendix, large intestine, and uterus and adnexa. The remaining 51 were abscesses present at the time of surgery (table II), and 17 of these arose from the appendix.

TABLE I—Sites and Underlying Diseases and Surgical Procedures associated with 149 Bacteroides Infections

Site	Underlying Diseases and Surgical Procedures	No. of Infections
Upper intestinal tract	Carcinoma of oesophagus (1), perforated duodenal ulcer (1), gastrojejunostomy (1)	3
Biliary tract ..	Cholangitis (1), cholecystitis (1)	2
Small intestine ..	Ischaemia (2), Crohn's disease (3)	5
Appendix ..	Acute appendicitis (19), perforated and gangrenous appendicitis (35), routine appendicectomy (4)	58
Large intestine ..	Ischaemia (3); diverticulitis (6); perforated diverticulitis (4); carcinoma of colon (8), rectum (2), caecum (1)	24
Uterus, adnexa ..	Uterine infection: post-partum (13), postabortal (3), pelvic infection (3), salpingitis (1); surgical infection: hysterectomy (8), postcaesarean section (2), oophorectomy (1)	31
Vulva, vagina ..	Vaginitis (3); surgical infection: episiotomy (4), Manchester repair and anterior colporrhaphy (3), carcinoma of vulva (2)	12
Urinary tract ..	Prostatectomy (2), carcinoma of bladder (1), vesicocolic fistula (1)	4
Skin ..	Pilonidal sinus (4), bedsores (3), gangrene of foot (1), fracture of foot (1), burns (1)	10

TABLE II—Site of Abscess and Source of Infection in 51 Cases

	No. of Cases		No. of Cases
Gastrointestinal (40 cases):	15	Genitourinary (9 cases):	3
Appendix	4	Pelvic, uterine origin ..	3
Pelvic	7	Pyosalpinx, tubo-ovarian ..	2
Diverticulitis ..	1	Pyometra ..	1
Carcinoma ..	1	Bartholin's gland ..	1
Appendix ..	2	Periurethral ..	1
Abdominal	8	Pyonephrosis ..	1
Diverticulitis ..	2	Miscellaneous (2 cases):	1
Carcinoma ..	1	Neck ..	1
Crohn's disease ..	1	Groin ..	1
Strangulated hernia ..	2		
Unknown ..	2		
Ischiorectal and rectal ..	5		
Perianal ..	4		
Subphrenic ..	1		

Bacteroides was found in pure culture in 112 (56%) of the specimens. In mixed culture it was associated with other Gram-negative bacilli in 76% of the isolations and with Gram-positive cocci in 15%. In 9% of the mixed cultures other anaerobic bacteria were present.

All strains isolated were *B. fragilis*. A pure growth was found more often in genitourinary infections (67%) than in infections of the intestinal tract (48%). The incidence of pure growth in appendicular infections fell from 52% without perforation to 26% where perforation had occurred. Malignancy was usually associated with a pure growth (75%).

Other bacteria were isolated in 88 cases (table III). *Klebsiella* species (39%), *Enterobacter* species (23%), and *Escherichia coli* (22%) were the most common Gram-negative bacilli and anaerobic streptococci the commonest Gram-positive cocci (10%).

Complications and Outcome.—Altogether 131 patients (65.5%) recovered but 59 (29.5%) developed complications and 10 died, five directly as a result of the infection and five from associated diseases. In the latter cases the infection played a significant part in the deaths. The mortality in this series was 5% overall but was 33% where bacteraemia was present and 2.7% where there was only a tissue infection. All the patients who died were over 60 years of age. The commonest complication was the development of metastatic abscesses but two patients developed thrombophlebitis and one became jaundiced. The incidence of complications was highest in intestinal infections (42%) and infections associated with malignancies (44%) and least with obstetric and gynaecological infections, 5% and 28% respectively.

Antibiotic Treatment.—Antibiotic treatment was given to 102 patients but in only 43 cases was the therapy effective against bacteroides. The recovery rates associated with the appropriate antibiotics used are shown in table IV. Clindamycin was the most effective antibiotic, with a recovery rate of 78%. This rate, however, was only slightly better than that found in the 142 patients who were untreated or received ineffective antibiotic therapy—that is, 93 patients (65%). The most commonly prescribed antibiotic in this series was ampicillin, which was given in 58 cases. In only five infections was the strain of bacteroides sensitive to concentrations readily attainable in the blood on standard dosage.

Postoperative Wound Infections.—During the three-year period 1970-72 there were 423 postoperative wound infections in a total of 3,852 major and intermediate grade abdominal operations, an incidence of 11% (table V). Of these infections 71 (17%) were caused by bacteroides in either pure or mixed culture. In the first six months of 1973 there were 95 wound infections in 753 operations, an incidence of 13%, and 77 (81%) of these were caused by bacteroides.

TABLE III—Other Bacteria associated with Bacteroides (88 Cases)

	No. (%) of Cases		No. (%) of Cases
Gram-negative:		Gram-positive:	
<i>Klebsiella</i> species ..	34 (39)	Anaerobic streptococci ..	9 (10)
<i>Enterobacter</i> species ..	20 (23)	β -Haemolytic streptococci ..	4 (5)
<i>Escherichia coli</i> ..	19 (22)	<i>Streptococcus faecalis</i> ..	3 (3)
<i>Proteus</i> species ..	11 (13)	<i>Staphylococcus albus</i> ..	2 (2)
<i>Pseudomonas aeruginosa</i> ..	4 (5)	Non-haemolytic streptococci ..	2 (2)
		<i>Clostridium welchii</i> ..	1 (1)

TABLE IV—Recovery Rates and Development of Complications in Bacteroides Infections treated with Appropriate Chemotherapy

Antibiotic	No. of Patients	Recovery	Complications
Clindamycin ..	18	14 (78%)	Abscess (2), persisting infection associated with intrauterine device (2)
Lincomycin ..	14	9 (64%)	Abscess (2), infection (2), death (1)
Tetracycline ..	11	5 (45%)	Abscess (3), infection (3)
Sulphonamide/trimethoprim ..	10	6 (60%)	Abscess (4)
Ampicillin ..	5	3 (60%)	Abscess (2)

Antibiotic Sensitivities.—The distribution of minimum inhibitory concentrations (M.I.C.s) of the nine chemotherapeutic substances against 106 strains of bacteroides are shown in the chart. Clindamycin and rifampicin had the greatest activity and over 90% of the strains were inhibited by 1 µg/ml. Tetracycline showed a bimodal distribution—whereas over 40% of the strains were sensitive to 0.5 µg/ml 25% required over 10 µg/ml for inhibition.

Distribution of minimum inhibitory concentrations of nine chemotherapeutic substances against bacteroides (106 strains). C=Clindamycin. R=Rifampicin. T=Tetracycline. M=Metronidazole. L=Lincomycin. E=Erythromycin. Ca=Carbenicillin. F=Fusidic acid. A=Ampicillin.

When the M.I.C.s were related to the expected blood concentrations on normal dosage (table VI) over 95% of the strains were sensitive to clindamycin, rifampicin, and metronidazole. Lincomycin was active when administered parenterally but with oral therapy only 63% of the strains were inhibited. Because of the high blood levels after parenteral administration carbenicillin was appreciably more active than parenteral ampicillin though there was little difference in the M.I.C.s.

TABLE V—Incidence of Bacteroides in Postoperative Wound Infections after Intestinal Surgery

	Total No. of Operations	Incidence of Wound Infections	Proportion of Infections containing Bacteroides
1970	1,200*	123 (10%)	16 (13%)
1971	1,272	145 (11%)	20 (14%)
1972	1,380	155 (11%)	35 (23%)
1973 (Jan.-June)	753	95 (13%)	77 (81%)

*Approximate total.

TABLE VI—Antibiotic Sensitivity of Bacteroides (M.I.C. Compared with Expected Blood Concentration on Standard Dosage)

	Route	% Sensitive Strains
Clindamycin	Oral	100
Rifampicin	Oral	97
Metronidazole	Oral	96
Lincomycin	I.M.	89
Carbenicillin	I.M.	85
Fusidic acid	Oral	70
Tetracycline	Oral	65
Lincomycin	Oral	63
Ampicillin	I.M.	57
Erythromycin	Oral	23
Ampicillin	Oral	9

I.M. = Intramuscular.

Discussion

Despite increasing numbers of reports on anaerobic infections reliable data on the true incidence of infection due to these organisms and particularly *B. fragilis* in postoperative wound

sepsis after intestinal surgery are lacking. Difficulties in isolation in the laboratory are undoubtedly major reasons why these organisms are not reported more often, and it is always necessary to use selective media to aid rapid identification. Perhaps more important than the laboratory techniques, as in this study bacteroides were isolated in pure growth from 56% of the wound swabs, is the care taken in the collection and transport of the specimen. In surgical treatment bacteriology often has only a secondary role, and an important swab from an intra-abdominal abscess may not be examined immediately and may even wait overnight before culture is carried out. The result of this is that oxygen-sensitive bacteria die and the most careful cultural techniques will fail to isolate them. If anaerobic bacteria are to be found in infected material it is vital that there be a minimum of delay between collection and laboratory examination.

In this study 200 infections have been described and, as reported by other workers (Gillespie and Guy, 1956; Gunn, 1956; Wilson *et al.*, 1972), 56% occurred after inflammation or disease of the gastrointestinal tract. The other major source of the infection was the genital tract, and in a small number of cases bacteroides were isolated in pure growth from cases of vaginitis, particularly the senile and atrophic types, and though the role of these organisms in this type of infection is not yet defined treatment rapidly resolved the symptoms.

In this study the infection was diagnosed in only 38% of the patients who had a swab taken at the time of surgery and it is likely that more care in the collection of these specimens would have increased this number. Bacteroides are rarely a cause of minor wound sepsis and in this study all infections were severe, suggesting that the wound infections were the result of contamination from the peritoneal cavity.

Bacteroides were isolated in pure growth in over half of the infections, and where a mixed growth was present the most common accompanying bacteria were *Klebsiella* and *Enterobacter* species, probably present as a result of the high incidence of preoperative ampicillin therapy. Gram-positive cocci were rarely seen and when present were usually anaerobic streptococci and not skin flora. Bacteroides are difficult to see in films except when they are present in large numbers, and even when Gram-negative bacilli are reported failure to isolate them may be explained by prior chemotherapy; 58 of the patients in this study received ampicillin, 22 in combination with other antibiotics.

The outcome of bacteroides infections is relatively good, as most patients recover without any special measures and even despite inappropriate antibiotic therapy. Nevertheless, 34% of the patients in this series did develop complications, usually metastatic abscess formation, which in 15% caused an appreciable increase in inpatient stay and required further surgery. Prompt diagnosis of the infection and appropriate antibiotic therapy may reduce or prevent these complications. The incidence of complications was greatest in infections from intestinal sources or where a carcinoma was present and lowest in obstetric infection. The development of bacteraemia was a poor prognostic feature and increased the mortality from 2.7% to 33%, a rate similar to that reported by other workers (Bodner *et al.*, 1970; Felner and Dowell, 1971; Wilson *et al.*, 1972). All the patients who died, however, were over 60 years of age and half of them had concurrent serious diseases which would have eventually been fatal.

Bacteroides have an individual antibiotic spectrum and are rarely sensitive to the commonly prescribed prophylactic chemotherapeutic agents such as the penicillins and the aminoglycoside group of antibiotics. In this study clindamycin was the most effective antibiotic (table IV), confirming the results of other workers (Bartlett *et al.*, 1972; Tracy *et al.*, 1972; Mitchell and Simpson, 1973). Some workers have used tetracycline (Ellner and Wasilauskas, 1971; Ledger *et al.*, 1971; Kagnoff *et al.*, 1972) but its efficacy is now in question as many (Bodner *et al.*, 1972; Kislak, 1972; Martin *et al.*, 1972; Okubadejo *et al.*, 1973) have reported a high incidence of resistance, and in this study only 65% of the strains were sensitive to easily attainable serum

concentrations. In less acute infections metronidazole is indicated because of its high bactericidal activity at concentrations attained in the blood (Nastro and Finegold, 1972; Whelan and Hale, 1973). Rifampicin though having a high degree of activity against bacteroides should probably be reserved for the treatment of tuberculosis. The activity of fusidic acid suggests that it may be effective in the local treatment of bacteroides infections.

The incidence of bacteroides in postoperative wound infections was significantly high and the increase over the study period to 81% was startling. The reasons for this increase are twofold—firstly, a greater awareness on the part of the surgeons to send operative samples from patients found to have infection at abdominal surgery, and, secondly, improvements in laboratory techniques and transportation of specimens throughout the hospital. A smaller increase in the isolation of all anaerobic bacteria with improved cultural methods has also been reported by Hoffman and Gierhake (1969).

Bacteroides infections, especially of postoperative wounds, appear to be largely preventable by antibiotic therapy. It is essential to obtain samples for bacteriological examination at the time of surgery. Early diagnosis of bacteroides infections will lead to appropriate antibiotic therapy being given and it is likely that many postoperative wound infections would be prevented. Clindamycin or lincomycin should always be included in the primary treatment of all suspected abdominal infections.

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Influence of Previous Oral Contraception and Maternal Oxytocin Infusion on Neonatal Jaundice

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Summary

A prospective study of serum bilirubin levels on the first and sixth days of life in a series of 181 infants has failed to provide evidence to suggest that previous maternal oral contraception, maternal oxytocin infusion, epidural anaesthesia, or breast-feeding are factors influencing neonatal jaundice.

Introduction

An increased incidence of neonatal jaundice has been noted in babies born to mothers who used oral contraceptives (Wong and

Wood, 1971; McConnell et al., 1973). One of us, however, failed to confirm this association in a preliminary survey (Barnardo et al., 1972). Wong and Wood (1971) related the increased incidence of jaundice to breast-feeding as well as to previous maternal oral contraception. By contrast, McConnell et al. (1973) related this to bottle-feeding and not to breast-feeding. The maternal infusion of oxytocic agents such as syntocinon has also been implicated as a cause of neonatal jaundice by some workers (Ghosh and Hudson, 1972; Davies et al., 1973), though this has not been found by others (McConnell et al., 1973).

In 181 mothers and neonates we have prospectively studied the relation between maternal and neonatal serum bilirubin levels, maternal oral contraceptive history, maternal exposure to oxytocic agents immediately preceding delivery, and the method of feeding in the first six days of life.

Methods

Consecutive single-birth deliveries in the obstetric unit, Queen Mary's Hospital, Roehampton, during a two-month period in mid-1973 were included in the study. Out of 209 mothers and neonates 28 were excluded for the following reasons: no bilirubin data (8), mixed feeding in the first six days of life (6), no information on previous oral contraception (5), neonatal

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