Incidence and Significance of Intraperitoneal Anaerobic Bacteria

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To amplify recent interest in anaerobic infections following abdominal disease, trauma, or surgery, 512 consecutive patients subjected to emergency celiotomy had both aerobic and anaerobic cultures taken of peritoneal fluid as well as all complicating wound and intra-abdominal infections. Average time between peritoneal entry or abscess drainage and specimen incubating under anaerobic conditions was less than two minutes. During 4 of the seven study months, patients had antibiotic therapy randomized, with clindamycin or cephalothin being sole parenteral agents and given intravenously prior to operation and for 5 days thereafter. Results demonstrated that anaerobes uniformly contaminate the peritoneal cavity whenever distal or obstructed intestine has been perforated, irrespective of the cause. Although all but one of the 123 complicating wound and intra-abdominal infections were due solely or at least in part to aerobic pathogens, ⅔ of such infections also contained one or more different anaerobic species acting in synergism with the aerobes. No significant difference in incidence of postoperative infection or in infecting bacteria could be found with respect to antibiotic administered or etiology of perforation. Indeed, duration of bacterial exposure to atmospheric oxygen was the most critical factor influencing culture recoverability of anaerobic organisms, likelihood of ensuing wound or peritoneal sepsis participated in by an anaerobe, and success in control of established infections harboring anaerobes.

COINCIDENT with the introduction of clindamycin into the market of prescription available antibiotics, interest in anaerobic bacteria and their attendant infections has been suddenly rekindled and has steadily increased.[18] Without doubt this new antibiotic is highly effective on *in vitro* testing against most species of anaerobes isolated from human infection and, in particular, *Bacteroides fragilis*.[5,9,10] In addition, it is now certain that anaerobic microorganisms play a more significant role in surgical infections than previously had been appreciated and that, accordingly, antimicrobial therapy directed specifically against anaerobes is often warranted.[1,2,4,7,12,13,15,17,18] Nevertheless, there is still a relative ignorance as to the frequency and importance of anaerobic bacterial participation in those septic states associated with intra-abdominal disease, trauma, and operation.[7,14]

Since the thorough literature review by Altemeier in 1938 and his clear documentation that both anaerobic and aerobic species of bacteria are responsible for peritonitis in perforative appendicitis, few reports have referred to anaerobic microbes being involved in infections that develop after peritoneal, pelvic, or perineal contamination by intestinal contents.[1,7] During the past four years, Gorbach and his associates have repeatedly stressed in several publications an almost routine soilage of the peritoneal cavity by anaerobes whenever gastrointestinal perforation has occurred because of disease or trauma.[7,17,18] Infections that subsequently follow such contamination have also been due to a multiplicity of bacterial species having both anaerobic and aerobic culture requirements. Indeed, this synergistic combination of aerobes and anaerobes has appeared to represent to some investigators a valid argument to support the polymicrobial basis, rather than a single species cause, for the majority of infections relegated to the surgical ward.[7]

Failure to deliver a proper specimen—promptly and under strict anaerobic conditions—to a bacteriology laboratory experienced and adequately equipped for anaerobe work has been the major reason for a lack of knowledge in this area.[5,7-10,17,18] At present, however, most medical centers do have the capacity for reasonably accurate anaerobic bacteriology, and thus the culprit now responsible for a report of "no anaerobic growth" may well be the sampler, that is the surgeon, himself. Even a delay of only a few minutes in inoculation of the speci-

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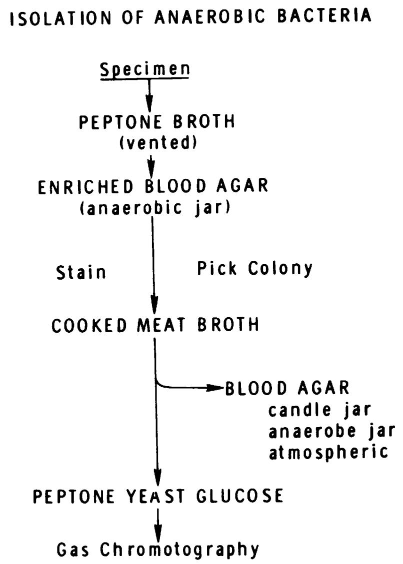

FIG. 1. Initial bacteriologic processing of anaerobic cultures.

men into an environment relatively devoid of oxygen can cause death of the very species of anaerobes that have invested a given infection with life-threatening virulence.

Clinical Study

During the seven month period from April 1 through October 31, 1973, all patients undergoing emergency celiotomy on the Trauma and Pediatric Surgical Services at Grady Memorial Hospital had anaerobic as well as aerobic cultures taken immediately upon peritoneal entry. The operating surgeon, after aspirating 1 or 2 ml of peritoneal fluid, then injected the specimen directly into a culture medium of supplemented peptone broth. A sterile venting unit was next inserted in order to allow for the escape of gases that would be generated by subsequent bacterial growth. Finally, the entire culture unit was then placed in a special incubator located within the operating room suite and maintained at 37C. Although there were more perfected means available for culturing anaerobically, this particular method offered the important advantages of simplicity and practicality for individuals not skilled in such techniques as roll-tube inoculation. In addition, almost immediate incubation was assured.

Several of the patients had repeated peritoneal cultures taken at half hour or hourly intervals throughout the course of their operation, with some samples being obtained even as late as 4 hours after the abdomen had been opened. Identical methods were also used for culture of all complicating wound and intra-abdominal infections that developed postoperatively in these same patients, with the incubator in the operating room area again serving as the central collecting point.

Any patient exhibiting signs or symptoms suggestive of associated bacteremia had both aerobic and anaerobic blood cultures drawn. These were then processed just as expeditiously as were the more routine wound and peritoneal cultures.

Bacteriology

Within 24 hours of inoculation, tubes containing the broth cultures were picked up from the operating room and processed for both aerobic and anaerobic growth. Aerobic bacterial species were isolated and identified according to standard laboratory procedures, while testing for antibiotic sensitivity was carried out by the commonly employed disc technique of Bauer, et al.[3]

Apparent anaerobic isolates were first confirmed as being true anaerobes and only then were further identified (Fig. 1). Genus was determined by a few simple bacteriologic tests and gas chromatography (Fig. 2). Methods generally conformed to those described by Holdeman and Moore.[8] Although speciation of all bacterial isolates was routinely done, it soon became obvious that, except for *Clostridia* and *Bacteroides fragilis*, de-

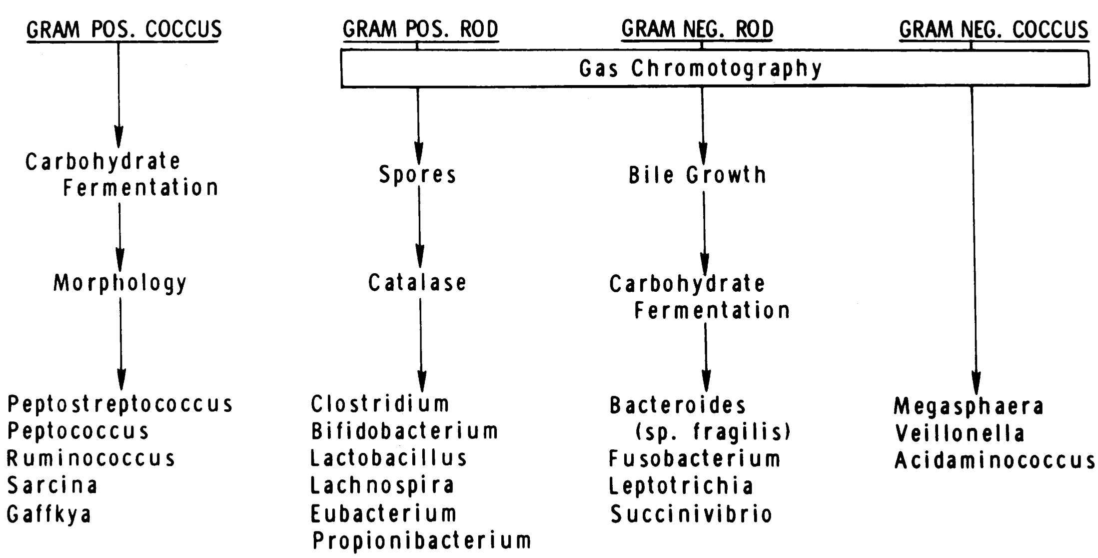

FIG. 2. Determination of the genus of anaerobic isolates.

	Patients	INCIDENCE OF INFECTION Wound	Abdominal
Routine Cephalothin	202	26%	8%
Random Cephalothin	163	15%	3%
Random Clindamycin	147	14%	3%
TOTAL SERIES	512	19%	5%

TABLE 1. Incidence of postoperative wound and intra-abdominal infections.

termination of exact anaerobic species was of little practical value in routine clinical practice. Tests of susceptibility to clindamycin and to cephalothin were later run on all anaerobic isolates by means of a replicator and agar-dilution techniques.[5,10]

Antibiotic Therapy

During the first 3 months, cephalothin was administered intravenously to all patients prior to, during, and for 5 days after operation. The usual dose was 2 gm given every 6 hours.

Randomization of intravenous antibiotics was then begun and continued throughout the last 4 months of the study. Patients with even hospital numbers received similar doses of cephalothin at the same intervals stated above. If, however the hospital number was odd, clindamycin was given intravenously on the same time schedule but at a dose of 300 mg. Evolution or worsening of sepsis seldom occurred prior to the fifth postoperative day; yet, when such did develop, an aminoglycoside (gentamicin or tobramycin) was added to the antibiotic regimen.

Tabulation

Results were analyzed on the basis of aerobic and/or anaerobic bacteria isolated, individual bacterial species, antibiotic sensitivity of these species, method of sampling, time of taking the specimen, source of the specimen, disease process accounting for the initial peritoneal contamination, incidence of later wound and peritoneal infection, species and frequency of complicating bacteremias, and antibiotic administered. Comparisons between initial peritoneal contaminants and bacteria responsible for subsequent infection were also drawn as were results and complications from use of the individual study antibiotics. Finally, an attempt was made to determine prevalence as well as importance of the anaerobic bacteria that so often contaminate the peritoneal cavity.

Results

During the 7 month study period, 512 patients underwent emergency celiotomy and provided the basic material for culture analysis (Table 1). There were 202 patients in the first three months when cephalothin was the routine antibiotic. During the 4 months of randomization, an additional 163 received cephalothin; while 147 were given clindamycin. No significant differences could be found between types of cases or incidence of infectious complications with respect to the randomized patients given different antibiotics. However, the initial study group composed of consecutive patients receiving cephalothin had a greater incidence of both wound and intra-abdominal sepsis than did either of the randomized groups during the ensuing 4 months. This discrepancy could be explained only in part and then on the basis of greater attention to operative technique and wound care as well as by a significant reduction in frequency of colon injuries during the summer and early fall months.

Complications of antibiotic administration were common. Local phlebitis developed in 18% of patients receiving cephalothin, and this generally remained symptomatic for at least 5 days after cessation of the intravenous drip. Clindamycin, on the other hand, was associated with such a severe enteritis in 7% or so pronounced a rash in another 14% that the drug had to be discontinued. Thus the overall rate of adverse reactions to antibiotic therapy were not significantly different between the various study groups.

Aerobic Bacteria

Almost half, that is 244 of the 512 patients, had at least one species of aerobic bacteria contaminating their peritoneal cavity at the time of initial operation. This gave an incidence of 47.7%. There were a total of 460 aerobic isolates from the abdomens of these 244 patients, thereby giving an average of 1.89 aerobic species per patient and a range of one to five different species.

The most commonly grown organism was *E. coli*, representing more than a third of all of the aerobic isolates (Table 2). The total number of remaining gram-negative rods amounted to an even greater proportion, that is 43%. Of the gram-positive species, *Enterococcus* was the one most frequently isolated.

Antibiotic susceptibility of the aerobic bacterial isolates demonstrated a consistent superiority of the aminoglycosides, only a fair activity of cephalothin, and essentially no benefit from clindamycin except against species of *Staphylococcus* (Table 3). Only carbenicillin and, to some degree, gentamicin offered any reliability of action against the *Enterococcus*.

Anaerobic Bacteria

At least one species of anaerobic bacteria was recovered at initial culture from the peritoneal cavity of 159 patients, thereby producing an incidence of 31.1%. These 382 anaerobic isolates averaged 2.4 per patient, with a range of one to nine different species per patient.

GRAM NEGATIVE RODS			GRAM POSITIVE COCCI		
E. coli	164	35.7%	Enterococcus	55	12.0%
Kleb-Entero.	78	17.0	Staphylococcus	13	2.8
Proteus	69	15.0	(sp. aureus	7	1.5)
Ps. aeruginosa	20	4.3	Streptococcus	11	2.4
Miscellaneous	29	6.3			
			FUNGI		
GRAM POSITIVE RODS			Candida	2	0.4%
Miscellaneous	16	3.5%	Other	3	0.7

TABLE 2. Aerobic bacteria isolated on initial culture of the abdomen (460 isolates from 244 patients).

There was a great variation as to anaerobic genera, although *Bacteroides* was by far the largest group, representing more than 35% (Table 4). *Bacteroides fragilis* alone accounted for 14%. *Eubacteria* made up the next most frequently encountered genus, but this designation often became a catch-all term for unspecified gram-positive rods. *Clostridia* were noted in just over 7% of the total isolates.

Antimicrobial sensitivity testing was carried out for only two antibiotics—cephalothin and clindamycin (Table 5). The superiority of clindamycin was almost uniform and was most impressive against isolates of *Bacteroides fragilis*.

Incidence of Anaerobes

The pathologic and clinical progression of appendicitis from a simple erythematous process, through suppuration and gangrene, to its final stage of perforation was reflected in the incidence of aerobic and anaerobic cultures being positive (Fig. 3). Going from simple to suppurative appendicitis, there was a gradual increase in the frequency of aerobic species culturable from the peritoneal fluid. However, anaerobes were almost never present until gangrenous changes had developed in the appendiceal wall. On gross perforation, anaerobes became in fact the dominant microbial flora.

Other types of peritonitis had variable frequencies of anaerobic participation (Fig. 4). For example, perforation of a gastric ulcer led to much greater bacterial contamination by both aerobes and anaerobes than did the same event complicating a duodenal ulcer. Cholecystitis and pancreatitis were primarily chemical reactions during their earlier stages, while pelvic inflammatory disease was often due in part to anaerobic bacteria.

Following penetrating abdominal trauma, perforating wounds of the colon and rectum almost uniformly caused contamination of the peritoneal cavity by both anaerobic as well as aerobic species (Fig. 5). Perforations of the stomach and small bowel produced a soilage that paralleled what had been noted for rupture of gastric and duodenal ulcers. On the other hand, duodenal perforations due to trauma and the absence of any gastrointestinal injury rarely if ever led to noticeable bacterial contamination.

The spill of bacteria into the peritoneal cavity during surgery was another interesting feature (Fig. 6). If enterolysis without inadvertent enterotomy could be accomplished for the relief of mechanical intestinal obstruction, cultures had essentially no growth. However, the spill of obstructed small bowel contents produced a contamination that equalled what resulted when intestine was already gangrenous and required resection. In con-

	Number of Isolates	ANTIBIOTIC AND DISC CONCENTRATION Gent. 10 mcg	Tobr. 10 mcg	Carb. 50 mcg	Ceph. 30 mcg	Chlor. 30 mcg	Kan. 30 mcg	Coly. 10 mcg	Clind. 2 mcg
E. Coli	164	99	99	89	65	95	81	96	0
Kleb-Enterobacter	78	100	100	27	41	95	86	91	0
Proteus	69	91	93	67	67	58	75	0	0
Ps. aeruginosa	20	95	95	80	0	0	0	100	0
Misc. Gram-neg. rods	29	97	97	79	52	90	83	93	0
Staphylococcus	13	100	92	85	100	—	—	—	100
Enterococcus	55	80	25	100	0	—	—	—	13

TABLE 3. Antibiotic sensitivity testing of initial aerobic bacterial isolates (Per cent of isolates sensitive).

TABLE 4. Anaerobic bacteria isolated on initial culture of the abdomen (382 isolates from 159 patients).

GRAM POSITIVE COCCI		
Peptostreptococcus	22	5.7%
Peptococcus	18	4.7
Ruminoccoccus	1	0.3
Sarcina	1	0.3
Gaffkya	1	0.3
GRAM POSITIVE RODS		
Clostridium	29	7.6%
Bifidobacterium	11	2.9
Lactobacillus	10	2.6
Lachnospira	1	0.3
Eubacterium	75	19.6
Propionibacterium	34	8.9
GRAM NEGATIVE COCCI		
Megasphaera	1	0.3%
Veillonella	15	3.9
Acidaminococcus	4	1.0
GRAM NEGATIVE RODS		
Bacteroides	136	35.6%
(sp. fragilis	54	14.1)
Fusobacterium	13	3.4
Leptotrichia	9	2.4
Succinivibrio	1	0.3

trast, performance of a colostomy seldom necessitated opening the bowel until after the abdomen had been closed. Accordingly, this operation was associated with only a minor incidence of soilage, primarily due to aerobic species alone.

Exposure to Air

Prolonged exposure of the abdomen, a wound, or even an abscess cavity to air significantly reduced the chances of isolating an anaerobe. For example, in cases of perforative gastrointestinal trauma, the incidence of anaerobic bacteria being cultured from peritoneal fluid diminished as the duration of exposure to atmospheric oxygen increased (Fig. 7). Although essentially all patients with colon wounds had initial contamination by anaerobes, such species of bacteria could be detected in only 10% one hour after the abdomen had been opened. Similar reductions in ability to detect the presence of anaerobes were noted in cases of gastric and small bowel perforation.

Even anaerobic bacteria actively participating in an established infection were susceptible to the adverse effects of atmospheric oxygen (Fig. 8). Although almost every specimen of peritoneal fluid from patients with

TABLE 5. Antibiotic sensitivity testing of initial anaerobic bacterial isolates.

ANAEROBE	NUMBER OF ISOLATES	ANTIBIOTIC TESTED mcg/ml	— PERCENT OF ANAEROBIC ISOLATES SENSITIVE— <0.1	0.2	0.4	0.8	1.6	3.1	6.2	12.5	25	50	>50
Gram Positive Cocci	43	Clind.	100	—	—	—	—	—	—	—	—	—	—
		Ceph.	51	58	74	91	93	98	98	100	—	—	—
Clostridium	29	Clind.	45	59	62	83	97	100	—	—	—	—	—
		Ceph.	34	59	66	69	79	97	100	—	—	—	—
Eubacterium	75	Clind.	57	79	85	89	96	99	100	—	—	—	—
		Ceph.	43	57	60	65	65	77	84	89	100	—	—
Propionibacterium	34	Clind.	100	—	—	—	—	—	—	—	—	—	—
		Ceph.	29	79	88	97	100	—	—	—	—	—	—
Bacteroides fragilis	54	Clind.	63	69	85	89	98	98	100	—	—	—	—
		Ceph.	11	11	11	17	17	17	20	39	76	87	100
Bacteroides species	82	Clind.	72	77	89	91	95	99	100	—	—	—	—
		Ceph.	20	29	33	33	38	39	39	54	87	94	100
Other Anaerobes	137	Clind.	45	61	65	81	94	98	98	98	100	—	—
		Ceph.	30	40	46	74	80	93	97	100	—	—	—

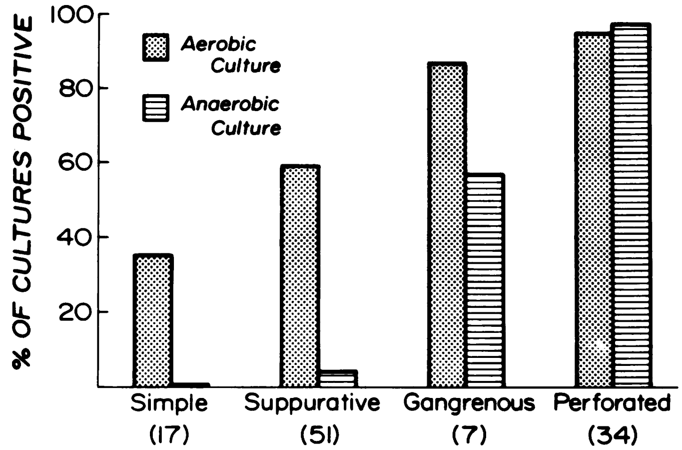

FIG. 3. Relative incidence of aerobic and anaerobic bacteria contaminating the peritoneal cavity of patients with appendicitis.

perforative appendicitis was positive for anaerobes if taken immediately upon surgical entry to the abdomen, this incidence fell to 30% by the end of one hour and to less than 10% after two hours.

A final example of the great sensitivity of anaerobic species to the adverse effect of oxygen in room air was noted when two different sampling methods were compared (Fig. 9). The recovery rate of anaerobes from specimens taken by a swab was only a fraction of what was obtained by aspiration and then immediate inoculation into an anaerobic medium.

Bacteriology of Infections

Irrespective as to the site of subsequent infection—be it wound or intra-abdominal—the frequency of anaerobe involvement was always significantly less than its relative population in the initial contaminant (Fig. 10). This reduction in incidence of participating anaerobes averaged 28%. It appeared that merely exposure of the wound or peritoneal cavity to atmospheric oxygen was the prime factor responsible for such a change.

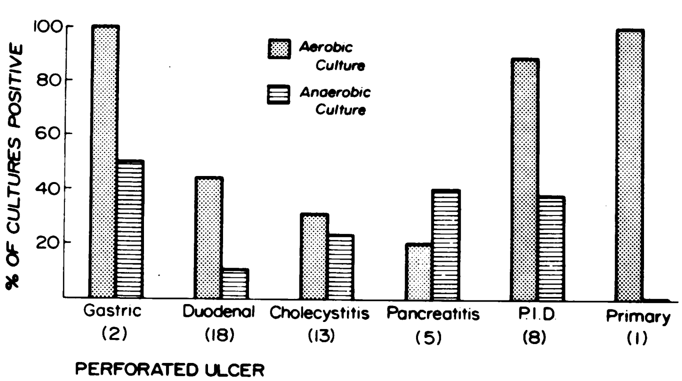

FIG. 4. Relative incidence of aerobic and anaerobic bacteria contaminating the peritoneal cavity of patients with various forms of peritonitis.

Complicating bacteremias developed in 21 patients (Table 6). Blood cultures yielded 69 different bacterial isolates, of which 21 or 30% were anaerobic species. In addition, it was noted that *Enterococcus* was more commonly grown from the blood than was *Bacteroides* with respect to both number of patients as well as total number of positive cultures.

No significant difference was found in frequency of aerobic or anaerobic bacterial participation in the postoperative wound and intra-abdominal infections when the two randomized treatment groups were compared (Fig. 11). This equality had not been created by case selection either, as both groups had similar proportions of aerobes and anaerobes contaminating the peritoneal cavity at the time of emergency celiotomy when initial cultures had been obtained. Likewise, there was no significant difference in the two groups of study patients, their diseases and injuries, associated medical conditions, or any other recognizable factor.

Discussion

Based upon previous reports as well as the present study, there appears to be irrefutable evidence that not only aerobic, but also anaerobic, bacteria uniformly contaminate the abdominal cavity whenever perforation of the colon or rectum has occurred.[1,2,4,7,17,18] In addition, since the intraluminal flora of obstructed intestine parallels that of the large bowel, spill of such contents automatically soils the peritoneum with identical microbes. Subsequent wound and intraperitoneal infections in these patients likewise harbor anaerobic as well as aerobic species. Such has always been the case, even though unrecognized until recently. However, only dedication to proper culture technique and perfected methods for

	Patients	Cultures
Gram neg. rods	11	23
Enterococcus	7	13
Bacteroides	6	9
Eubacterium	4	6
Peptostreptococcus	4	4
Clostridium	2	2
Candida	1	3
Other	3	9
TOTALS	21	69

TABLE 6. Bacteria isolated from blood cultures in septic patients (Positive blood cultures in 21 patients).

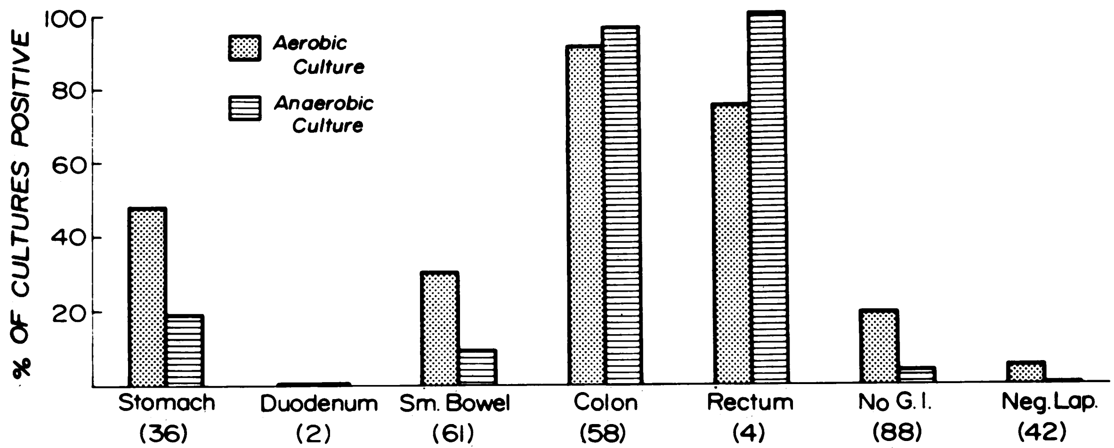

FIG. 5. Relative incidence of aerobic and anaerobic bacteria contaminating the peritoneal cavity of patients with penetrating abdominal trauma.

anaerobe isolation and identification will permit these events to be more thoroughly appreciated.

Sampling Techniques

Anaerobes vary considerably in their susceptibility to the lethal effects of oxygen. Often the most virulent species contributing to a mixed infection dies before the specimen of pus can be properly inoculated and placed under strict anaerobic conditions. Thus, results of bacteriologic tests may well be false and fail to reflect the true microbial components of the infection. Accordingly, any sample to be processed for anaerobic growth should be taken quickly and with minimal contact to atmospheric oxygen. Aspiration of pus with a large bore needle and syringe is usually the easiest and most efficient method of sampling.

Next, the specimen must be inoculated into prereduced media and under anaerobic conditions as soon as possible.[8] Anaerobic blood culture media, that is prereduced broths, are ideal. They require no expertise in roll-tube techniques or in any additional piece of equipment, such as the CO_2 pack or similar items. All necessary media can be conveniently stocked in any hospital area, have a long shelf life, and are generally adaptable to any member of the health team for almost every clinical situation.

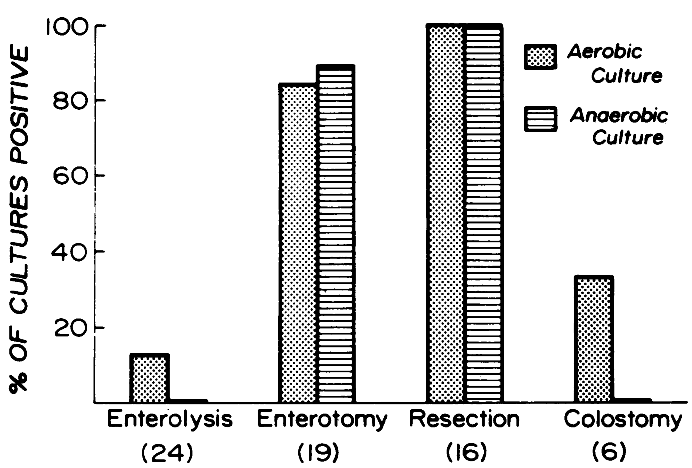

FIG. 6. Relative incidence of aerobic and anaerobic bacteria contaminating the peritoneal cavity of patients with intestinal obstruction.

Finally, the specimen should be incubated immediately at 37C. Otherwise, important species of anaerobes may be lost; for cold retards their cellular metabolism and thereby augments overgrowth by other and less virulent anaerobes.[8]

Requisites of Anaerobic Infection

Anaerobes can exist and propagate only when local oxidation-reduction potential has been significantly reduced. Such environments having a generally diminished oxygen tension are provided by necrotic tissue and marked local ischemia. These, despite being the more obvious and certainly the most classical manifestations of anaerobic infection, represent the extremes and account for only a small fraction of sepsis due to anaerobic species.[15]

By far the most common infections due, at least in part, to anaerobes are those that evolve as a synergism between aerobic and anaerobic bacteria. Growing in symbiosis, two of more different bacterial species with entirely opposite oxygen requirements may so alter the local environment by their metabolic end-products that conditions in the immediate vicinity become exceedingly conducive to survival and even rapid proliferation of the synergistic partners.[11,12,15] Careful culture techniques by other investigators as well as methods used in the present study have consistently shown that the great majority of wound and intraabdominal infections complicating disease, trauma, or surgery of the gastrointestinal tract are based upon this symbiotic relationship.[1,7,17,18] Indeed, strict anaerobe sepsis is rare, and even infections due solely to one or more aerobic gram-negative rods are probably uncommon under these conditions.

Some combinations of aerobic and anerobic species have significantly greater virulence than do others, and thus the respective infections that they create likewise

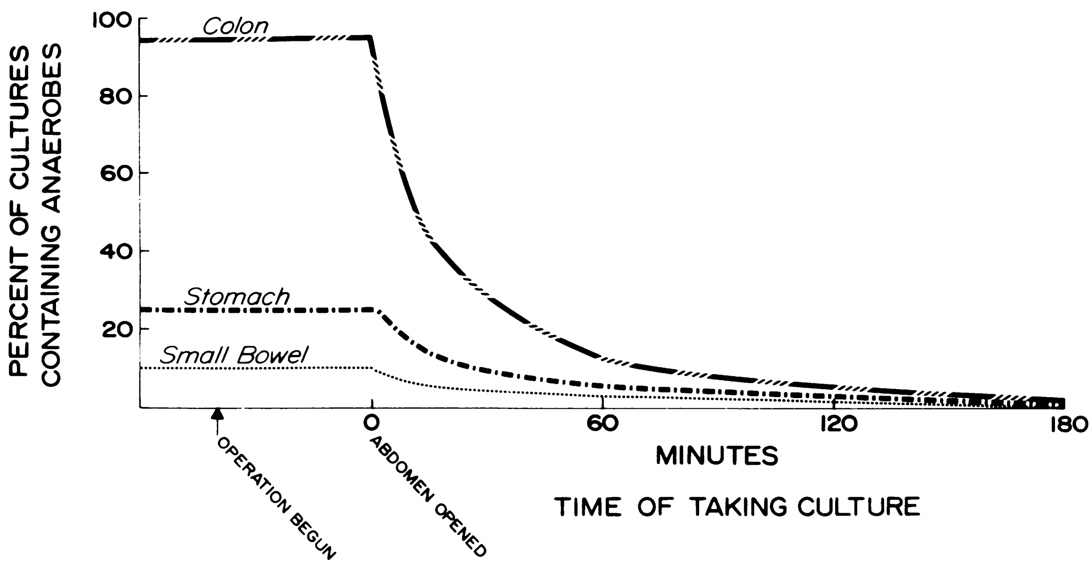

FIG. 7. Recoverability of anaerobes from the peritoneal cavity of patients with penetrating intestinal trauma.

vary in severity. However, the most critical factors determining patient susceptibility and progression of a given bacterial synergism are those associated diseases that limit host resistance. Diabetes mellitus, derangements in liver and kidney function, generalized occlusive vascular disease, extremes of age, obesity, and malnutrition appear to be the more detrimental of all precipitating diseases.[2,4,7,12,13,15] Indeed, symbiotic infections in such individuals are so severe that specific names have been used to describe variations in anatomic location and responsible bacterial species.[7,11,12,15]

Diagnosis of Anaerobic Infections

Since most anaerobic infections are in truth polymicrobial synergisms and since the majority encountered on any surgical service have evolved after disease, trauma, or surgery of the gastrointestinal tract, the basic clinical features are what have been described for many years as characteristics of gram-negative sepsis.[7,14] However, there are definite alterations in this pattern whenever anaerobic species contribute significantly to the sepsis. Fevers are higher and tend to spike; the patient is irrational; and jaundice may be present.[15] Any one of these three additions should greatly increase suspicion that anaerobes are involved.

The wound itself has certain characteristics that are diagnostic. A putrid, often nauseating, odor is readily detected.[7,15] Almost without exception, such unpleasant aromas are caused by gases produced only through anaerobic bacterial metabolism. In addition, the pus has a "dishwater" appearance because of a minimal number of leukocytes contained within.[15] So-called "creamy" pus is packed with phagocytes, and only an active blood circulation locally can bring such corpuscular elements to the immediate area of infection. In contrast, gangrenous tissue or an environment replete with anaerobes characteristically has a poor vascular supply and thus a relative paucity of white blood cells.

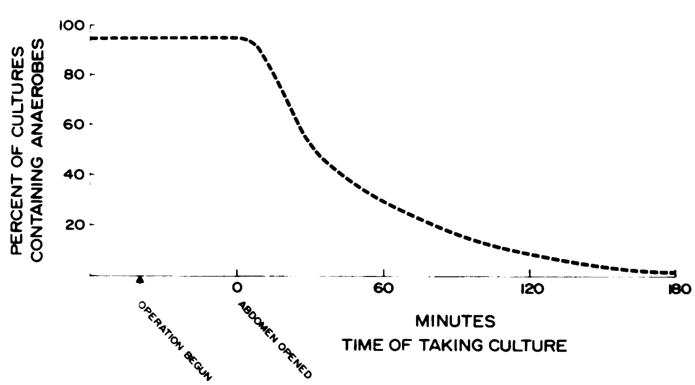

FIG. 8. Recoverability of anaerobes from the peritoneal cavity of patients with perforated appendicitis.

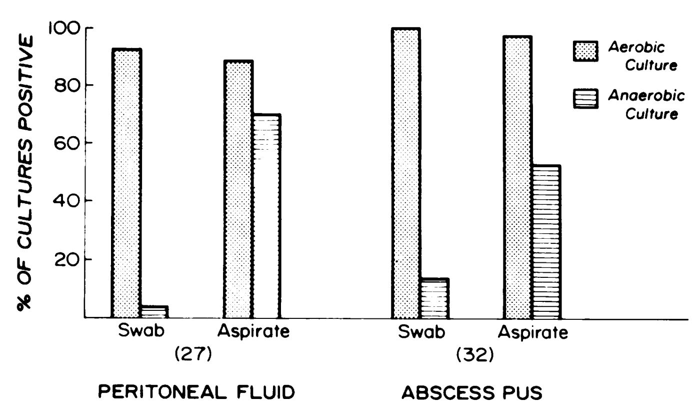

FIG. 9. Relative incidence of aerobic and anaerobic bacteria recoverable from the contaminated peritoneal cavity and from established infections of the wound or abdomen.

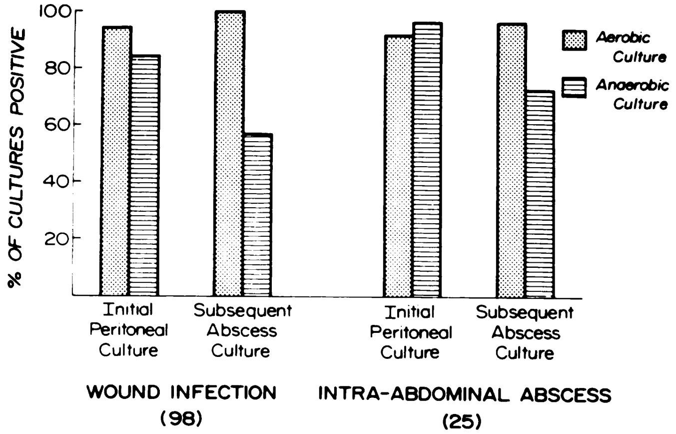

FIG. 10. Comparison of initial peritoneal cultures and subsequent infections in the same patients.

Principles of Treatment

Success in treatment of anaerobic infections revolves around two basic considerations: 1) alterations in local environment so as to impair or even kill the infecting anaerobes; and 2) administration of antimicrobial agents with specific activity against anaerobic species. There are many variations on these simple principles, yet all other measures of therapy are merely supportive unless based upon such tenets.

One way to change the local environment and thereby to preclude continued anaerobe survival is excision of all necrotic tissue and conversion of the infectious process to an open wound. Redox potentials are significantly increased by exposure to atmospheric concentrations of oxygen. Nevertheless, viable anaerobes may persist if aerobic species in the immediate vicinity can maintain a local, yet considerable, decrease in the oxidation-reduction potential. This dependency of anaerobic species on their aerobic counterpart probably explains the response, even though transient, of mixed infections in non-gangrenous tissues, such as the peritoneal cavity, to therapy with antibiotics active only against aerobic pathogens (Fig. 12). Elimination of the aerobic partner automatically increases the redox potential and thereby converts the area of infection to a hostile, oxygen-rich environment. Such may also explain the apparent equality of the two regimens of antibiotic therapy randomized in the present study.

An old colloquialism in surgery states that patients with peritonitis usually improve whenever "the abdomen had been opened to let sunshine in." This is in part a valid observation, and its application has benefitted many patients with peritonitis. However, the correction of anatomic defects, removal of purulent material, and, finally, direct exposure of abdominal parietes to atmospheric oxygen have undoubtedly produced the desired clinical improvement, not any beam of light.

Antibiotics Specific Against Anaerobes

Although *in vitro* tests have revealed that a number of presently available antibiotics are highly effective against most species of anaerobic bacteria, clinical or *in vivo* response is entirely dependent upon the antimicrobial reaching the actual sites of infection.[14] Ischemic or frankly gangrenous tissues have been deprived of an adequate blood supply and therefore can essentially never acquire bactericidal concentrations of parenterally administered antibiotics. Thus, administration of an antibiotic active against anaerobic species can be of real value only: 1) in cases of bacterial synergism, that is when metabolism of the symbiotic aerobe has permitted infection by the anaerobe despite excellent circulation locally; and 2) in cases where an anaerobe bacteremia has complicated either a pure or mixed infection. It is only under these conditions that antibiotic can be delivered to infected tissues or a body cavity.

From a practical point of view, administration of antibiotics effective against anaerobic bacteria is always indicated if an anaerobic bacteremia has complicated the septic process. Such is almost certain to have occurred if no initial or lasting response is obtained by therapeutic doses of an aminoglycoside in cases of mixed infection or when one or more signs of anaerobic sepsis—high spiking fevers, irrational behavior, and jaundice—persist.

Probably the only other worthwhile reason to administer a specific parenteral antibiotic is when debridement or drainage of the infection must be delayed because of an as yet unrecognized source of infection, patient deterioration requiring energetic supportive measures prior to anesthesia, or some similar consideration. Although the patient may improve dramatically following such antibiotic therapy, recurrence of sepsis is an absolute certainty unless gangrenous tissues are debrided and the infection is converted to an open wound by either spontaneous or surgical drainage. There can be no substitute for this latter event; it is the mainstay of definitive therapy.

Of the several antibiotics with proven effectiveness

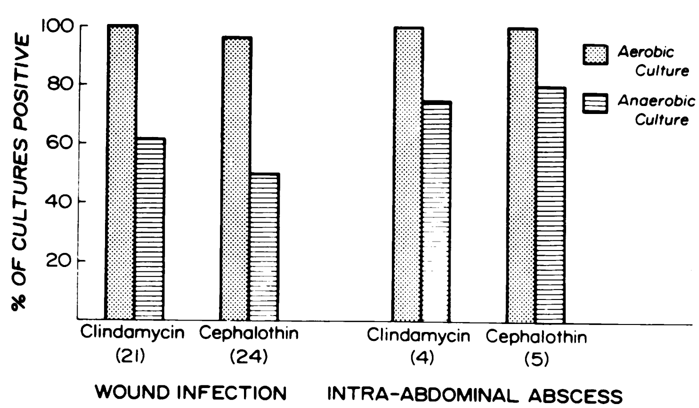

FIG. 11. Comparison of bacterial flora from patients receiving cephalothin and clindamycin.

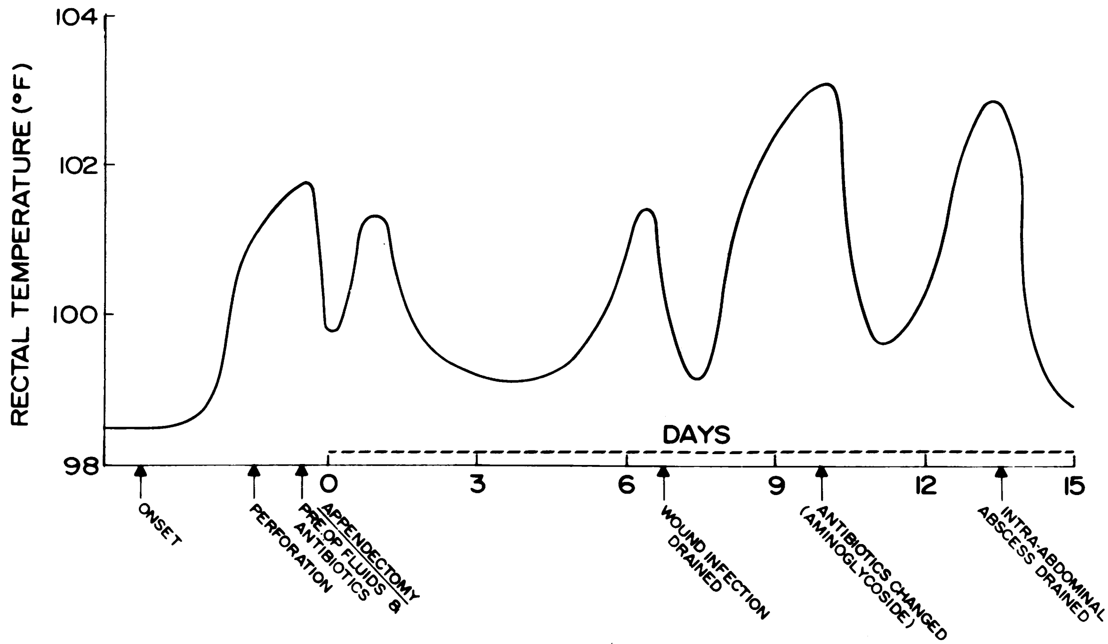

FIG. 12. Septic course of a patient treated for perforated appendicitis.

against anaerobes, erythromycin-related compounds appear at present to be the most reliable.[2,4,5,7,9,10,13,17,18] Clindamycin certainly provides more certain coverage for all possible species, although erythromycin may well be its equal under clinical or specific laboratory conditions where tissue pH is within the physiologic range of 7.0 to 7.5.[5,10] Other systemic antimicrobials that have been used in the past are chloramphenicol and tetracycline. Without doubt, chloramphenicol is the superior agent.

Unfortunately, use of clindamycin is associated with significant complications.[6,7,16] Troublesome rashes are common, but the most dangerous of all its adverse reactions is the diarrhea that develops in approximately 20% of cases and the even more serious pseudomembranous colitis. This latter has been noted in almost 10% of all patients receiving a course of clindamycin, whether the antibiotic had been given parenterally or by mouth.[16] Indeed, deaths have been documented as being directly attributable to this one complication.[6,16] Thus, institution of clindamycin therapy should not be taken lightly and should be considered only if signs and symptoms indicate with considerable certainty that anerobic bacteremia is present or an established anaerobic infection has as yet been poorly controlled.

References

1. Altemeier, W. A.: The Bacterial Flora of Acute Perforated Appendicitis with Peritonitis. Ann. Surg., 107:517, 1938.
2. Baird, R. M.: Postoperative Infections from Bacteroides. Amer. Surg., 39:459, 1973.
3. Bauer, A. W., Kirby, W. M. M., Sherris, J. C., and Tuck, M.: Antibiotic Susceptibility Testing By a Standardized Single Disc Method. Am. J. Clin. Pathol., 45:493, 1966.
4. Beazley. R. M., Polakavetz, S. H., and Miller, R. M.: Bacteroides Infections on a University Surgical Service. Surg. Gynecol. Obstet., 135:742, 1972.
5. Brier, G., Wolny. J., and Griffith. R. S.: A Micro-dilution Technic for the Susceptibility Testing of Anaerobic Bacteria. Unpublished data. Lilly Laboratory for Clinical Research, Indianapolis.
6. Cohen, I. E., McNeil, C. J., and Wells, R. F.: Clindamycin-Associated Colitis, JAMA, 223:1379, 1973.
7. Gorbach, S. L. and Bartlett, J. G.: Anaerobic Infections. New Eng. J. Med., 290:1177, 1237 & 1269, 1974.
8. Holdeman, L. V. and Moore, W. E. C.: *Anaerobe Laboratory Manual.* VPI Anaerobe Laboratory, Blacksburg, Va., 1972.
9. Kislak, J. W.: The Susceptibility of Bacteroides fragilis to 24 Antibiotics. J. Infect. Dis., 125:295, 1972.
10. Martin, W. J., Gardner, M., and Washington, J. A., III: In Vitro Antimicrobial Susceptibility of Anaerobic Bacteria Isolated from Clinical Specimens. Antimicrob. Agents Chemother, 1:148, 1972.
11. Meleney, F. L.: Hemolytic Streptococcus Gangrene. Arch Surg., 9:317, 1924.
12. Rea, W. J. and Wyrick, W. J., Jr.: Necrotizing Fasciitis. Ann. Surg., 172:957, 1970.
13. Rissing, J. P., Crowder, J. G., Dunfee, T., and White, A.: Bacteroides Bacteremia from Decubitus Ulcers. South. Med. J., 67:1179, 1974.
14. Stone, H. H. and Hester, T. R., Jr.: Incisional and Peritoneal Infection after Emergency Celiotomy. Ann. Surg., 177:669, 1973.
15. Stone, H. H. and Martin, J. D., Jr.: Synergistic Necrotizing Cellulitis. Ann. Surg., 175:702, 1972.
16. Tedesco, F. J., Barton, R. W., and Alpers, D. H.: Clindamycin-Associated Colitis: A Prospective Study. Ann. Intern. Med., 81:429, 1974.
17. Thadepalli, H., Gorbach, S. L., Broido, P., and Norsen, J.: A Prospective Study of Infections in Penetrating Abdominal Trauma. Am. J. Clin. Nutr., 25:1405, 1972.
18. Thadepalli, H., Gorbach, S. W., Broido, P. W., et al.: Abdominal Trauma, Anaerobes, and Antibiotics. Surg. Gynecol. Obstet., 137:270, 1973.

Discussion

DR. HIRAM C. POLK, JR. (Louisville, Kentucky): The paper Dr. Stone has presented, I think, will become *the* definitive work in this field, just as the work he shared with us on fungal sepsis in the surgical setting a year ago. I would make a couple of comments quickly: the quantitation that's been accomplished in Dr. Stone's study is extremely well done, and the value of the concurrent control, I think, in clinical