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MINIREVIEW

Therapeutic Implications of Bacteriologic Findings in Mixed Aerobic-Anaerobic Infections

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INTRODUCTION

Mixed infections involving anaerobic and aerobic or facultative bacteria typically involve a complex flora so that results of cultures are not available for some time. Accordingly, initial therapy of such infections must be empiric, although information such as that derived from examination of a Gram stain may be used effectively to modify the usual empiric approach. The physician should base the initial choice of therapeutic agents on the nature and location of the infectious process, the usual flora anticipated in infections of the type being treated, factors that might have modified such flora, Gram stain results, and the severity of the infection.

PROBLEMS WITH CLINICAL ANAEROBIC BACTERIOLOGY

Anaerobic bacteria grow more slowly than aerobic or facultative forms, but the primary factors accounting for delayed reporting of results are the facts that the vast majority of anaerobic infections are mixed and that it takes considerable time to recover all the components of a complex infecting flora in pure culture and then to identify them. Accordingly, it may take several days to several weeks for a definitive bacteriology laboratory report. There are additional problems to consider. Difficulties in obtaining optimum specimen collection and transport may lead to inaccurate and even misleading results. Failure to exclude normal flora during the course of specimen collection may lead to considerable extra time being required to analyze the specimen and to inaccurate data being furnished to the clinician. On the other hand, improper transport may lead to loss of viability of anaerobes so that certain organisms are not recovered at all or are recovered in reduced numbers and are therefore considered to be relatively unimportant. Some clinical laboratories are not doing reliable anaerobic bacteriology; culture results from such laboratories may mislead clinicians. The cost of detailed anaerobic bacteriology is high because it is labor intensive; some laboratories capable of doing good, definitive work must do less-than-thorough bacteriology for economic reasons. Finally, it should be appreciated that in a specimen that yields five to six anaerobes and three to four nonanaerobes, it may be difficult to judge the relative importance of the different isolates (S. M. Finegold and M. A. C. Edelstein, *in* J. M. Hardie and S. P. Borriello, ed., *Anaerobes Today*, in press).

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ASPIRATION PNEUMONIA

Aspiration pneumonia is the most common hospital-acquired pneumonia and is relatively common in the community setting as well. It is almost invariably a mixed infection involving various elements of the oral flora and, at times, the gastric flora as well. The gastric flora is discussed below. The normal oral flora consists of various streptococci, chiefly species of the viridans group, and a variety of nonsporeforming anaerobes. Among the latter are various *Bacteroides*, *Fusobacterium* (especially *Fusobacterium nucleatum*), and *Peptostreptococcus* species. Among the *Bacteroides* species encountered are the pigmented species, *Bacteroides oris* and *B. buccae* (formerly known as *B. ruminicola*), the *B. oralis* group, the *B. ureolyticus* group, *B. bivius*, *B. disiens* and, to a limited extent, the *B. fragilis* group. The term "pigmented *Bacteroides*" is a convenient way to refer to various species, at least 13 currently, originally all classified as *B. melaninogenicus* and subsequently as three subspecies of that organism. Among the more commonly encountered pigmented *Bacteroides* are *B. melaninogenicus* per se, *B. asaccharolyticus*, *B. intermedius*, *B. gingivalis*, *B. loescheii*, *B. denticola*, and *B. endodontalis*. Patients in the hospital setting, especially those receiving antimicrobial therapy, commonly undergo oral colonization with nosocomial pathogens such as *Staphylococcus aureus*, various members of the family *Enterobacteriaceae*, and *Pseudomonas* species. In the case of hospital-acquired aspiration pneumonia, then, one must consider the possibility of the latter pathogens in addition to the indigenous oral anaerobes and streptococci (6).

INTRA-ABDOMINAL INFECTIONS

In anticipating the flora that might be encountered in various intra-abdominal infections, one must be aware of the normal flora that are encountered in various locations in the gastrointestinal tract and that may serve as the source of organisms for intra-abdominal infections. In the stomach, the flora is quite sparse in the absence of disease or medication that modifies the normal low pH or otherwise changes the flora. At normal pHs, there are typically only about 100 organisms per ml of gastric juice; these are chiefly streptococci, lactobacilli, and yeasts and may represent swallowed oral flora (5). At a pH of 7, the counts of gastric organisms rise to 10^6 to 10^7 (5). Disease states such as bleeding or obstructing peptic ulcer, gastric ulcer, or gastric carcinoma lead to a much greater colonization of the stomach and a more diverse flora that includes members of the family *Enterobacteriaceae* and anaerobes (20). Even the *B. fragilis* group may be encountered under these circumstances. The

duodenum also has a relatively sparse flora normally. As one proceeds down the intestinal tract, the number and variety of bacteria encountered increase. In the distal ileum, bacterial counts are of the order of 10^4 to 10^6, and flora is composed of both coliforms and various anaerobes (5). Again, disease of the small bowel, particularly that involving an element of obstruction, may affect the counts and variety of microorganisms significantly.

The colonic flora has been studied more extensively. It is much more profuse and diverse than is the small-bowel flora. Microbial counts are higher in the distal colon than in the ascending or transverse colon. Studies of the fecal flora, indicative of the situation in the distal colon, revealed total counts averaging 10^{12}/g of feces (dry weight) (8). Anaerobes outnumbered nonanaerobes by a factor of 1,000 to 1. The *B. fragilis* group is the dominant group in the normal flora of the large bowel. (It is important to differentiate between the species *B. fragilis* and the *B. fragilis* group as a whole. *B. fragilis* is the most commonly encountered species in this group and may be more virulent than the other species in the group [2], but there are over 10 species in the group altogether. Other species in the *B. fragilis* group encountered relatively frequently clinically include *B. thetaiotaomicron*, *B. distasonis*, *B. vulgatus*, and *B. ovatus*. The first three of the latter species, especially *B. thetaiotaomicron*, are not uncommonly relatively resistant to antimicrobial agents—usually more so than the species *B. fragilis*.) *B. thetaiotaomicron* was the most common species isolated from feces in the aforementioned study; it was found in 86% of 141 subjects studied, with a mean count of $10^{10.7}$/g. Other species in this group found frequently and in high counts in the feces included *B. vulgatus*, *B. distasonis*, *B. fragilis*, and *B. ovatus*. Other anaerobes prevalent in the normal fecal flora include *Eubacterium*, *Bifidobacterium*, and *Clostridium* species and anaerobic cocci. Lactobacilli are also fairly prevalent. Among the nonanaerobes, *Escherichia coli* and various streptococci, primarily enterococci, predominate.

In intra-abdominal infections, specimens yield an average of six organisms (four anaerobes and two nonanaerobes) each. *E. coli* and streptococci predominate among the nonanaerobes; the *B. fragilis* group, other *Bacteroides* species, *Peptostreptococcus* species, and clostridia predominate among the anaerobes.

BILIARY TRACT INFECTIONS

Biliary tract infections are considered separately from other intra-abdominal infections because the bacteriology is quite different. *E. coli* (and sometimes other members of the family *Enterobacteriaceae*, such as *Klebsiella* species) and enterococci are the predominant isolates from biliary tract infections. *Clostridium perfringens* is not encountered often but may lead to devastating results if appropriate therapy is not used. In certain patients, particularly those in older age groups and those with repeated biliary tract infections and/or unrelieved biliary tract obstruction, the *B. fragilis* group may also be important.

FEMALE GENITAL TRACT INFECTIONS

The organisms typically encountered in female genital tract infections include *Peptostreptococcus* species, group A and B and other streptococci, *C. perfringens* and other clostridia, *E. coli* and other coliforms, and *Actinomyces* or *Eubacterium* species (the latter particularly in association with intrauterine devices [G. B. Hill, J. C. Catignani, C. H. Thomann, D. E. Dzubay, A. P. Kohan, and O. M. Ayers, Program Abstr. 25th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1076, 1985]). The *B. fragilis* group and other *Bacteroides* species, especially *B. bivius* and *B. disiens*, may play an important role. In the case of pelvic inflammatory disease, gonococci and *Chlamydia* species are often found as well.

OTHER MIXED INFECTIONS

There are many other types of mixed anaerobic infections, but the examples cited above are the ones most commonly encountered. The flora of other types of anaerobic infections may be deduced from the original source (typically the mucosal surfaces of the oral cavity, bowel, or female genital tract) or may be found in various reference materials (such as reference 6).

SIGNIFICANCE OF VARIOUS ELEMENTS OF THE INFECTING FLORA

Among the nonanaerobes, members of the family *Enterobacteriaceae*, pseudomonads, *S. aureus*, various streptococci other than enterococci, gonococci, and *Chlamydia* species are all generally significant pathogens. Enterococci may be as well, of course, but they are generally less important than other organisms in mixed infections without bacteremia in nonimmunocompromised hosts (17, 22). Among the anaerobes, various *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*, and *Clostridium* species are generally important pathogens. Among the *Bacteroides* species, the *B. fragilis* group is clearly important, both from the standpoint of frequency of recovery from infection (21) and because of resistance to many antimicrobial agents. However, there is not adequate information on which to judge the relative importance of species within this group other than the species *B. fragilis*; they are isolated with some frequency from mixed infections. The availability of a drug, cefotetan, which has good activity against the species *B. fragilis* but poor activity against a number of other species of the *B. fragilis* group may permit further assessment of the significance of the latter organisms. Other, less commonly encountered anaerobes, such as *Actinomyces* species and some *Eubacterium* species, are also important. The other nonsporeforming anaerobic gram-positive bacilli are nonpathogenic, with rare exceptions. The relative importance of different organisms in a given mixed infection may be judged from such information as relative numbers of each strain present, presence in a pure culture, presence in the bloodstream, and persistence in repeated cultures.

FACTORS MODIFYING INDIGENOUS FLORA

In choosing empiric therapy on the basis of the indigenous flora that is likely to be involved in a given type of infection, the physician must take into account various factors that might lead to the modification of this flora. Several examples of such modification have already been cited—oral colonization with nosocomial pathogens in the hospital setting, obstructing or bleeding peptic ulcer, achlorhydria, etc. In general, the most important factor in the modification of indigenous flora is the administration of antimicrobial agents.

OTHER CONSIDERATIONS IN EMPIRIC THERAPY

In addition to knowledge of the normal flora and how it may be modified under certain conditions, one may use

information obtained from Gram staining of suitable specimens to choose initial empiric therapy more intelligently. In addition to indicating the type of organisms present, Gram staining provides information on quantitation and on the reliability of the specimen; it also serves as an important quality control feature for the laboratory. Other clues (e.g., foul odor, sulfur granules) may suggest the involvement of anaerobes or specific anaerobes.

PRINCIPLES OF THERAPY

Whenever surgical therapy (debridement, drainage, elimination of dead space, etc.) is indicated, it must be carried out. In the absence of proper surgical management, even appropriate surgical therapy may fail. With good surgical therapy, the patient may do well without antimicrobial agents or with less-than-optimum medical management. In terms of antimicrobial agents, it must be remembered that most anaerobic infections are mixed; if the agent chosen for the anaerobes does not provide adequate coverage for the nonanaerobes that may be present, an additional agent must be used. Other factors that may need to be considered in certain circumstances include central nervous system penetration and bactericidal effect. Clearly, the toxicity of various agents under consideration for therapy will be an important consideration. The impact on the normal flora is also of consequence; agents that produce relatively little disturbance of indigenous flora are less likely to lead to significant superinfection. In this connection, one major superinfection to be kept in mind is pseudomembranous colitis. This process is usually caused by *C. difficile*, although other clostridia and *S. aureus* may cause it on occasion. Agents that suppress normal colonic flora significantly and have relatively poor activity against *C. difficile*, of course, are more likely to lead to this complication. The cost of the various antimicrobial agents that may be suitable in terms of activity is certainly an important factor; to be considered in determining cost are pharmacokinetic characteristics that may permit less frequent dosing than is true for other agents.

The issue of breakpoint (the level of drug at or below which infection with the organism in question will generally respond to therapy, usually equivalent to peak levels achievable in serum with the maximum approved dosage) is a controversial one. It must be remembered that certain drugs are commonly given at dosages lower than the maximum dosage; in this case, it is likely that a smaller percentage of infections involving strains of certain resistant organisms, such as the *B. fragilis* group, will respond to conventional therapy than to maximal therapy and that therefore, in effect, the breakpoint should be lower.

Finally, the severity of infection is a factor that should be taken into account. One should not use the most potent of all agents for lesser infections; this is likely to lead to the development of resistance eventually and to the consequent loss of an important agent for serious infections. Less effective agents may be perfectly adequate for less severe infections in patients with good host defense mechanisms; indeed, one may not be able to demonstrate any advantage for a more potent agent in such a setting. For example, young, otherwise healthy patients with a community-acquired infection such as appendicitis and without generalized peritonitis or with pelvic inflammatory disease will usually respond well to agents with less activity in in vitro tests than to the best agents, provided that needed surgical management is carried out (24). If these less effective agents have other advantages, such as low toxicity, low cost, etc., it makes good sense to use them. On the other hand, a hospital-acquired intra-abdominal infection in an elderly diabetic in an intensive-care unit demands the use of the very best antimicrobial agents available.

SPECIFIC ANTIMICROBIAL THERAPY

Aminoglycosides are generally poorly active or inactive against anaerobic bacteria, except for *B. gracilis* and a number of *Peptostreptococcus* strains. Sulfonamides and co-trimoxazole have no role in the therapy of anaerobic infections at present, and currently available quinolone agents have relatively poor activity against anaerobes.

Penicillin G still maintains good activity against many clinically important anaerobes if one accepts a breakpoint of 16 U/ml; the *B. fragilis* group is a major exception. There are a number of other *Bacteroides* species and other anaerobes that produce beta-lactamases in amounts sufficient to result in resistance. These include the *B. fragilis* group, the pigmented *Bacteroides* group, *B. oris*, *B. buccae*, the *B. oralis* group, *B. disiens*, *B. coagulans*, *B. hypermegas*, *B. multiacidus*, *F. nucleatum*, *F. mortiferum*, *F. varium*, *C. ramosum*, *C. clostridiiforme*, and *C. butyricum*. Accordingly, penicillin G cannot be depended on as single drug therapy in serious anaerobic infections. It may be used in less severe infections initially, pending observation of the patient's response and perhaps availability of laboratory data concerning the susceptibility of anaerobic isolates. Ampicillin, penicillin V, and amoxicillin are comparable to penicillin G in overall effectiveness against anaerobes but may be better for oral dosing because of better levels in blood in some cases. Methicillin, nafcillin, and the isoxazolyl penicillins (oxacillin, dicloxacillin) are all inferior to penicillin G in effectiveness against anaerobes. Broad-spectrum penicillins such as carbenicillin, ticarcillin, and piperacillin, have good activity in vitro at the high levels achievable in blood with these agents, and clinical studies have yielded good results (9, 23).

The earlier cephalosporins (e.g., cephalothin, cefazolin, cephradine) have poor activity against the *B. fragilis* group but fairly good activity against other anaerobes. A later group of cephalosporins (cefamandole, cefuroxime, and cefonicid) has relatively poor activity against the *B. fragilis* group, but cefoxitin is much more active (12). There has been the development of resistance to cefoxitin by the *B. fragilis* group in a number of centers (4, 25). It should also be noted that one-third of strains of clostridia other than *C. perfringens* are resistant to cefoxitin (7). Data on the activity of cefoxitin and of more recently introduced cephalosporins, penicillins, and other beta-lactam agents against recent isolates of various anaerobes from the Veterans Administration Wadsworth Medical Center are presented in Tables 1 to 3. The activity of ceftizoxime varies with the susceptibility test conditions (K. E. Aldridge, H. M. Wexler, C. V. Sanders, and S. M. Finegold, 27th ICAAC, abstr. no. 336, p. 154, 1987). However, clinical results in patients with pelvic infections and intra-abdominal infections have been good (10, 19). Imipenem has excellent activity against virtually all anaerobes in vitro and has been very effective in clinical studies (15).

The activities of a number of non-beta-lactam antimicrobial agents (as compared with penicillin G) are presented in Table 4. Erythromycin is less active than penicillin G against important anaerobes. Most strains of the *B. fragilis* group are resistant, as are more than half of the fusobacteria. Tetracycline is no longer useful for most anaerobic infec-

TABLE 1. Activity of various drugs against *Bacteroides* species

Drug	Breakpoint (μg/ml)	% of the following species susceptible at the breakpoint:			
		B. fragilis species	*B. fragilis* group[a]	*B. gracilis*	Other
Chloramphenicol	16	100	100	100	100
Imipenem	8	100	100	100	100
Ampicillin-sulbactam[b]	16	100	100	NT[c]	100
Metronidazole	16	100	100	93	99
Clindamycin	4	93	81	61	100
Cefoxitin	32	92	75	78	99
Piperacillin	128	84	85	78	97
Cefotaxime	32	50	50	78	96
Ceftizoxime	32	43	45	89	97
Cefoperazone	32	57	51	67	94
Moxalactam	16	78	55	78	77
Cefotetan	32	85	56	NT	80
Penicillin G	10	5	6	67	70

[a] Includes the species *B. fragilis*.
[b] Similar combinations presently available are amoxicillin plus clavulanic acid and ticarcillin plus clavulanic acid; they have comparable activities.
[c] NT, Not tested.

tions because of the development of resistance on the part of most types of anaerobic bacteria (3). Doxycycline is only a little more active but may be suitable for long-term therapy of mild to moderately severe infections, such as certain forms of actinomycosis, if the initial response is good. Vancomycin has not been formally studied in anaerobic infections other than intestinal infections involving *C. difficile*, but it does have good activity against gram-positive anaerobic organisms.

Chloramphenicol remains active against virtually all anaerobes, but now the MICs for the *B. fragilis* group commonly are close to the breakpoint for that drug. Clindamycin remains quite active against most anaerobes, but there has been a significant development of resistance, particularly among members of the *B. fragilis* group (25). Data from the Veterans Administration Wadsworth Medical Center are given in Tables 1 to 3. Ten percent of anaerobic cocci

TABLE 2. Susceptibility of anaerobes other than *Bacteroides* species to antimicrobial agents

Drug	% of the following species susceptible at the breakpoint:			
	Fusobacterium	Anaerobic cocci	*Clostridium*	Nonsporeforming gram-positive rods
Chloramphenicol	100	100	100	97
Imipenem	95	100	100	100
Ampicillin-sulbactam[a]	97	100	100	100
Metronidazole	100	98–99	99	63
Piperacillin	99	100	100	100
Clindamycin	92	97	90	86
Cefoxitin	99	100	65	95
Cefotaxime	100	100	100	90
Ceftizoxime	100	100	100	87
Cefoperazone	88	100	100	84
Moxalactam	77	100	100	73
Cefotetan	81	100	100	100
Penicillin G	100	100	100	97

[a] Similar combinations presently available are amoxicillin plus clavulanic acid and ticarcillin plus clavulanic acid; they have comparable activities.

TABLE 3. Susceptibility of *C. difficile* to antimicrobial agents

Drug	% Susceptible at the breakpoint[a]
Chloramphenicol	72
Imipenem	100
Ampicillin-sulbactam	100
Metronidazole	100
Piperacillin	100
Clindamycin	8
Cefoxitin	0
Cefotaxime	0
Ceftizoxime	0
Cefoperazone	5
Moxalactam	8
Cefotetan	96
Penicillin G	100

[a] The breakpoint is used only as a reference point. Factors important in determining likely therapeutic usefulness or risk of inducing *C. difficile*-associated enteric disease include the level of the drug achieved within the colon lumen and the impact on indigenous colonic flora.

formerly classified in the genus *Peptococcus* (and now classified in the genus *Peptostreptococcus*) are resistant to clindamycin, and 20 to 30% of strains of a number of *Clostridium* species other than *C. perfringens* are resistant to this agent. Metronidazole has excellent activity against all anaerobes other than some of the cocci (especially those that are not obligate anaerobes); it has poor activity against gram-positive nonsporeforming rods (including *Actinomyces* and *Arachnia* species) (7).

Beta-lactamase inhibitors have been introduced recently to overcome the problem of resistance to beta-lactam agents related to the production of beta-lactamases. There are presently three combinations of a beta-lactam agent and a beta-lactamase inhibitor on the market—amoxicillin plus clavulanic acid, ticarcillin plus clavulanic acid, and ampicillin plus sulbactam. Other combinations are undergoing investigation. These combinations show impressive activity in vitro (16) (Tables 1 to 3) and have done well in clinical trials (13).

Regimens for specific disease entities can be selected on the basis of the usual bacteriology of the disease process, how that bacteriology may have been modified by specific circumstances (such as a hospitalized patient, surgery, and antimicrobial therapy), and the usual anitmicrobial spectrum of the various agents that may be considered (taking into account such factors as the resistance patterns in the particular hospital or community, the pharmacologic properties of the drugs, toxicity, cost, etc.). There will usually be several options available.

Aspiration pneumonia acquired in the community setting, unless the patient is severely ill, can usually be managed successfully with penicillin G (in a dosage of 10 million to 15 million U/day for an average-sized adult with normal renal function). If the patient does not respond well or relapses, the addition of metronidazole or clindamycin to the regimen should result in a good response (assuming that appropriate bacteriologic studies do not indicate the presence of such organisms as staphylococci or nonanaerobic gram-negative bacilli). Although 30% of non-*B. fragilis*-group *Bacteroides* species are resistant to penicillin G (primarily on the basis of beta-lactamase production) (26), such organisms are usually only part of a relatively complex infecting flora, and patients harboring such organisms may still respond well to penicillin G, particularly if their general health has been relatively good up to that point. Hospital-acquired aspiration pneumo-

TABLE 4. In vitro susceptibility of anaerobes to antimicrobial agents

Bacteria	Activity[a] of:						
	Chloramphenicol	Clindamycin	Erythromycin[b]	Metronidazole	Penicillin G	Tetracycline	Vancomycin[b]
Microaerophilic and anaerobic cocci	+++	++ to +++	++ to +++	++	+++ to ++++	++	+++
B. fragilis group	+++	++ to +++	+ to ++	+++	+	+ to ++	+
Other *Bacteroides* spp.	+++	+++[c]	++ to +++	+++	++ to +++	++	+
Fusobacterium spp.	+++	++ to +++	+	+++	+++ to ++++	++ to +++	+
C. perfringens	+++	+++[d]	+++	+++	+++[d]	++	+++
Other *Clostridium* spp.	+++	++	++ to +++	+++	+++	++	++ to +++
Actinomyces spp.	+++	+++	+++	+ to ++	++++	++ to +++	++ to +++

[a] +, Poor or inconsistent; ++, moderate; +++, good; ++++, good with good pharmacologic characteristics and low toxicity, indicating the drug of choice.
[b] Not approved by the Food and Drug Administration for anaerobic infections.
[c] A few strains are resistant.
[d] Rare strains are resistant.

nia, as indicated earlier, may involve *S. aureus* and various resistant nonanaerobic gram-negative rods in addition to oral anaerobes and streptococci. For seriously ill patients in this category, one good regimen is metronidazole plus penicillin G for anaerobic coverage as well as other agents for the nonanaerobes that would be resistant (e.g., methicillin or vancomycin for *S. aureus* and ceftazidime and an aminoglycoside for the gram-negative bacilli). There are several other reasonable options, including imipenem or ticarcillin-clavulanic acid with or without the addition of an aminoglycoside or vancomycin, depending on the frequency of occurrence of resistant *Pseudomonas aeruginosa* or methicillin-resistant *S. aureus*. Clindamycin plus penicillin G could be used in lieu of metronidazole plus penicillin G. For less seriously ill patients, depending on the specific bacteriology, other regimens that might be suitable include cefoxitin (perhaps with an aminoglycoside initially until bacteriologic data are available) or a broad-spectrum penicillin such as piperacillin (perhaps with antistaphylococcal coverage added) or chloramphenicol (alone or supplemented). For patients who are not very ill, penicillin G is suitable for an initial trial for coverage against anaerobes and streptococci. It is true that penicillin may be less effective than it previously was in some pulmonary (and orofacial or other) infections involving oral anaerobes (11, 18), but the majority of patients will respond well.

In intra-abdominal infections, again, there are many options, and the severity of illness and the possible presence of resistant nosocomial organisms play a role in decisions concerning initial empiric therapy. In very sick patients (not necessarily very sick from the intra-abdominal infection per se but from, e.g., underlying or associated diseases, nutritional status, etc.), one good regimen includes metronidazole plus penicillin G for the anaerobic flora (and other agents such as ceftazidime with or without an aminoglycoside for gram-negative nonanaerobic rods and an antistaphylococcal agent, if indicated by Gram stain or other data). Because of the increased incidence of resistance of the *B. fragilis* group to clindamycin, cefoxitin, and piperacillin in many locations, these agents are not recommended as first-line antianaerobic therapy unless it is clear that resistance is not a problem where the patient is being treated. Imipenen, ticarcillin-clavulanic acid, and chloramphenicol are all reasonable choices for anaerobic coverage, to be supplemented if needed. In patients who are not very ill, there are a number of choices, including clindamycin or cefoxitin (perhaps supplemented with penicillin G to cover resistant anaerobic cocci and clostridia) or piperacillin, each to be supplemented as needed for the rest of the infecting flora when additional bacteriologic data become available or based on the patient's condition or response. In young, previously healthy individuals with perforated appendicitis without generalized peritonitis or with pelvic inflammatory disease and with proper surgical management when needed, agents that appear to be less active in vitro against anaerobes may be entirely effective clinically, as noted earlier.

Therapeutic approaches to other types of mixed anaerobic infections can be worked out in the same way. The usual bacteriology of the process, how it may be modified by various factors, the activity of the various drugs in vitro against the anaerobes (and other organisms) that are anticipated, and other characteristics of the drugs previously discussed are all taken into account in devising a therapeutic regimen.

SUSCEPTIBILITY TESTING

A number of problems occur in the susceptibility testing of anaerobic bacteria. These include a lack of standardization of techniques, choice of breakpoints, failure to use recent clinical isolates, testing too few strains, nonrepresentative species choices, clustering at the breakpoint, and the need for clinical correlation. Variations in testing procedures between laboratories have led to confusion regarding the extent of resistance among anaerobes. A standard, reproducible method of agreed-upon breakpoints would be extremely helpful in comparing data from different centers and in interpreting their significance. The current National Committee for Clinical Laboratory Standards method is unsatisfactory in that the medium does not support the growth of a number of strains of clinically important anaerobes, such as the pigmented *Bacteroides*, *F. nucleatum*, and anaerobic cocci. The phenomenon of clustering of endpoints within one dilution of the breakpoint is relatively common with certain beta-lactam agents, clindamycin, and chloramphenicol (25). Since the error factor common to most of the procedures used is one twofold dilution, this clustering effect may lead to significant variability, even within the same laboratory. The broth disk elution procedure, a simple test preferred by many clinical laboratories, has given poor results with certain newer cephalosporins (14). In the case of ceftizoxime, there is the additional problem of widely divergent results from different laboratories using different in vitro testing techniques (Aldridge et al., 27th ICAAC).

Susceptibility testing of anaerobes should be done (i) to determine the activity of new agents, (ii) to monitor suscep-

tibility patterns periodically in various centers (3), (iii) to monitor susceptibility patterns within a particular hospital or community, and (iv) to assist in the management of infections in individual patients. In the last case, indications would be failure, relapse, persistence of infection despite empiric therapy, and seriously ill patients or situations (such as brain abscesses, endocarditis, osteomyelitis, and infected prosthetic devices or vascular grafts) requiring prolonged therapy.

Although it is true that there is a need for better standardization of antimicrobial susceptibility testing for anaerobes, a great deal of valuable information has been accumulated on the activity of various drugs against different anaerobic pathogens. Unfortunately, there are no simple answers as to the "best" or "correct" test to use for in vitro susceptibility testing. The two most practical tests available for studying small numbers of isolates in clinical laboratories are the broth disk elution procedure and the broth microdilution test (the latter is available commercially in frozen form in microdilution trays with large numbers of wells already containing serial twofold dilutions of various antimicrobial agents). However, the broth disk elution procedure is not recommended for use with cefoxitin or ceftizoxime (14). Agar plate dilution procedures appear to be reasonably dependable, but further standardization is needed and, as noted previously, the National Committee for Clinical Laboratory Standards reference method does not allow the growth of all anaerobes.

Despite all of the above, the information available from these studies provides us with good guidance for empiric therapy. There are considerable clinical data that show a good correlation with in vitro data, although there is clearly a need for more correlative studies, particularly with certain newer agents and with older agents to which significant resistance has developed. Animal studies may be useful (1, 9).

LITERATURE CITED

1. **Bartlett, J. G., M. Dezfulian, and K. Joiner.** 1983. Relative efficacy and critical interval of antimicrobial agents in experimental infections involving *Bacteroides fragilis*. Arch. Surg. **118**:181–184.
2. **Brook, I.** 1986. Encapsulated anaerobic bacteria in synergistic infections. Microbiol. Rev. **50**:452–457.
3. **Cuchural, G., and F. P. Tally.** 1982. Factors affecting the choice of antimicrobial therapy for anaerobic infection. J. Antimicrob. Chemother. **10**(Suppl. A):11–22.
4. **Cuchural, G. J., Jr., F. P. Tally, N. V. Jacobus, S. L. Gorbach, K. Aldridge, T. Cleary, S. M. Finegold, G. Hill, P. Iannini, J. P. O'Keefe, and C. Pierson.** 1984. Antimicrobial susceptibilities of 1,292 isolates of the *Bacteroides fragilis* group in the United States: comparison of 1981 with 1982. Antimicrob. Agents Chemother. **26**:145–148.
5. **Drasar, B. S., and M. J. Hill.** 1974. Human intestinal flora. Academic Press, Inc. (London), Ltd., London.
6. **Finegold, S. M., W. L. George, and M. E. Mulligan.** 1986. Anaerobic infections. Year Book Medical Publishers, Inc., Chicago.
7. **Finegold, S. M., and R. D. Rolfe.** 1983. Susceptibility testing of anaerobic bacteria. Diagn. Microbiol. Infect. Dis. **1**:33–40.
8. **Finegold, S. M., V. L. Sutter, and G. E. Mathisen.** 1983. Normal indigenous intestinal flora, p. 3–31. *In* D. J. Hentges (ed.), Human intestinal microflora in health and disease. Academic Press, Inc., New York.
9. **Gorbach, S. L., and K. McGowan.** 1981. Comparative clinical trials in treatment of intra-abdominal sepsis. J. Antimicrob. Chemother. **8**(Suppl. D):95–104.
10. **Harding, G., J. Vincelette, A. Rachlis, I. Fong, L. Mandell, R. Feld, and D. Bailey.** 1982. A preliminary report on the use of ceftizoxime vs. clindamycin/tobramycin for the therapy of intra-abdominal and pelvic infections. J. Antimicrob. Chemother. **10**(Suppl. C):191–192.
11. **Heimdahl, A., L. Von Konow, and C. E. Nord.** 1980. Isolation of beta-lactamase-producing *Bacteroides* strains associated with clinical failures with penicillin treatment of human orofacial infections. Arch. Oral. Biol. **5**:689–692.
12. **Heseltine, P. N. R., T. V. Berne, A. E. Yellin, M. A. Gill, and M. D. Appleman.** 1986. The efficacy of cefoxitin vs. clindamycin/gentamicin in surgically treated stab wounds of the bowel. J. Trauma **26**:241–245.
13. **Jones, F. E., M. A. Malangoni, C. Spiegel, C. Edmiston, A. P. Walker, and R. E. Condon.** 1987. Antibiotic management of intra-abdominal sepsis. Infect. Surg. **6**(Suppl.):15–24.
14. **Jones, R. N., A. L. Barry, P. C. Fuchs, and S. D. Allen.** 1987. Ceftizoxime and cefoxitin susceptibility testing against anaerobic bacteria: comparison of results from three NCCLS methods and quality control recommendations for the reference agar dilution procedure. Diagn. Microbiol. Infect. Dis. **8**:87–94.
15. **Kager, L., and C. E. Nord.** 1985. Imipenem/cilastatin in the treatment of intraabdominal infections: a review of worldwide experience. Rev. Infect. Dis. **7**(Suppl 3):S518–S521.
16. **Lamothe, F., F. Auger, and J.-M. Lacroix.** 1984. Effect of clavulanic acid on the activities of ten beta-lactam agents against members of the *Bacteroides fragilis* group. Antimicrob. Agents Chemother. **25**:662–665.
17. **Ledger, W. J.** 1986. Infection in the female, 2nd ed. Lea & Febiger, Philadelphia.
18. **Levison, M. E., C. T. Mangura, B. Lorber, E. Abrutyn, E. L. Pesanti, R. S. Levy, R. R. MacGregor, and A. R. Schwartz.** 1983. Clindamycin compared with penicillin for the treatment of anaerobic lung abscess. Ann. Intern. Med. **98**:466–471.
19. **Lou, M. A., D. F. Chen, M. Bansal, S. Balasubramaniam, and H. Thadepalli.** 1982. Evaluation of ceftizoxime in acute peritonitis. J. Antimicrob. Chemother. **10**(Suppl. C):183–189.
20. **Nichols, R. L., and J. W. Smith.** 1975. Intragastric microbial colonization in common disease states of the stomach and duodenum. Ann. Surg. **182**:557–561.
21. **Polk, B F., and D. L. Kasper.** 1977. *Bacteroides fragilis* subspecies in clinical isolates. Ann. Intern. Med. **86**:569–571.
22. **Solomkin, J. S., and S. H. Dougherty.** 1984. The role of enterococci and *Candida* in intraabdominal infection, p. 17–36. *In* R. L. Simmons and A. I. Henriksen (ed.), Topics in intraabdominal surgical infection (part 2). Prentice-Hall, Inc., Englewood Cliffs, N.J.
23. **Sweet, R. L., M. O. Robbie, M. Ohm-Smith, and W. K. Hadley.** 1983. Comparative study of piperacillin versus cefoxitin in the treatment of obstetric and gynecologic infections. Am. J. Obstet. Gynecol. **145**:342–349.
24. **Ward, A., and D. M. Richards.** 1985. Cefotetan. A review of its antibacterial activity, pharmacokinetic properties and therapeutic use. Drugs **30**:382–426.
25. **Wexler, H. M., and S. M. Finegold.** 1987. Antimicrobial resistance in *Bacteroides*. J. Antimicrob. Chemother. **19**:143–146.
26. **Wexler, H. M., and S. M. Finegold.** 1987. *In vitro* activity of selected antibiotics against anaerobes. Clin. Ther. **10**(Suppl. A):12–18.