ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, March 1978, p. 416-418
0066-4804/78/0013-0416$02.00/0

Vol. 13, No. 3
Printed in U.S.A.

Susceptibility of *Campylobacter fetus* to Twenty-Two Antimicrobial Agents

ANTHONY W. CHOW,* VALERIE PATTEN, AND DOMINICK BEDNORZ

Department of Medicine, Harbor General Hospital, Torrance, California 90509; and University of California School of Medicine, Los Angeles, California 90024*

Received for publication 11 October 1977

In vitro susceptibility of 11 recent clinical isolates of *Campylobacter fetus* to 22 antimicrobial agents was determined by an agar dilution technique. Unlike most obligate anaerobic gram-negative bacilli, *C. fetus* isolates tested were relatively resistant to penicillin and cephalosporins, but exquisitely susceptible to tetracyclines and aminoglycosides. All strains were also inhibited at concentrations achievable in serum by clindamycin, chloramphenicol, metronidazole, carbenicillin, ticarcillin, and with rare exceptions, ampicillin. They were variably susceptible to lincomycin and erythromycin and highly resistant to vancomycin.

Campylobacter fetus, a microaerophilic, curved, gram-negative bacillus, has been increasingly associated with human disease (9). This may in part be attributed to improved anaerobic culture techniques, which also facilitate recovery of microaerophilic pathogens from clinical specimens. Clinical manifestations of *C. fetus* infections are protean, including septicemia (9), endocarditis (14), septic arthritis (12), dysentery (15), meningoencephalitis (10), mycotic aneurysm (14), and thrombophlebitis (22). Antimicrobial therapy is often difficult due to the relapsing nature of infection (2). Furthermore, well-standardized antimicrobial susceptibility of this organism has only been reported for limited strains of clinical isolates and with relatively few antibiotics (3, 4). In this present study, the in vitro susceptibility of 11 recent clinical isolates of *C. fetus* was determined by an agar dilution technique against 22 antimicrobial agents.

MATERIALS AND METHODS

All 11 strains of *C. fetus* in this study were recovered from clinical specimens since 1974 (blood, nine; pleural fluid, one; ascitic fluid, one). Test organisms were stored in 20% skim milk and frozen at −75°C until ready for susceptibility testing. All isolates were identified to subspecies level according to Holdeman and Moore (11), including demonstration of unipolar, single flagellum by a modified Leifson's flagellar stain (11). The most common subspecies was *intestinalis* (six isolates), followed by *jejuni* (four isolates) and *fetus* (one isolate).

Susceptibility testing with all antimicrobial agents was performed on Mueller-Hinton agar (Difco Laboratories, Detroit, Mich.), which had been adjusted to pH 7.2 and enriched with 5% defibrinated sheep blood and 0.1% (vol/vol) vitamin K-hemin. Twofold serial dilutions of penicillin (USP), ampicillin (Bristol), cephalothin (Lilly), cephalexin (Lilly), cefazolin (Lilly), cefaclor (Lilly), cefoxitin (Merk, Sharp & Dohme), cefamandole (Lilly), carbenicillin (Roerig), ticarcillin (Beecham-Massengil), clindamycin (Upjohn), lincomycin (USP), erythromycin (USP), tetracycline (USP), doxycycline (Pfizer), minocycline (Lederle), chloramphenicol (USP), metronidazole (Searle), gentamicin (USP), kanamycin (USP), amikacin (Bristol), and vancomycin (USP) susceptibility test powders were added. Test organisms in skim milk were inoculated into peptone-yeast glucose broth (Difco), streaked for purity and growth characteristics, subcultured for 48 h, and adjusted to a MacFarland no. 1 nephelometer standard (1), previously determined to approximate 10^6 to 10^7 organisms per ml by colony counting. Inocula (0.0025 ml) were delivered with a Steers replicating apparatus (18). Plates were then incubated at 37°C in anaerobic jars after two-thirds of the volume had been evacuated and replaced with a gas mixture containing 80% nitrogen-10% hydrogen-10% carbon dioxide. Anaerobic, microaerophilic, and aerobic plates without antibiotics were used for controls. All results were read at 48 h, and the minimum inhibitory concentration (MIC) recorded was the least antimicrobial concentration that yielded no visible growth.

RESULTS

The median MICs and cumulative percentages of strains of *C. fetus* inhibited at various concentrations of the 22 antimicrobial agents tested are presented in Tables 1 and 2. No difference in susceptibility between respective subspecies of *C. fetus* was noted, and, hence, results were combined.

C. fetus was relatively resistant to penicillin and all cephalosporins tested. Ampicillin, carbenicillin, and ticarcillin were considerably more active, and, except for one strain highly resistant

TABLE 1. *Susceptibility of C. fetus to penicillin, ampicillin, cephalothin, carbenicillin, vancomycin, and related antibiotics*

Drug	Median MIC (μg/ml)	Cumulative % strains inhibited at various concn (μg/ml)							
		1.2	2.5	5	10	20	40	80	≥160
Penicillin (11)[a]	10			36	54	100			
Ampicillin (10)	1.8	30	70	90					100
Cephalothin (10)	11.2			20	30	80		90	100
Cephalexin (10)	14				20	60	80	100	
Cefazolin (10)	14				10	60	90		100
Cefaclor (10)	6		10	40	60	90			100
Cefoxitin (10)	53				10	30	40	70	100
Cefamandole (10)	19					40	90		100
Carbenicillin (6)	4.6			17	83		100		
Ticarcillin (10)	2.6			60	90		100		
Vancomycin (10)	>40						0	NT[b]	NT

[a] Number of strains tested.
[b] NT, Not tested.

TABLE 2. *Susceptibility of C. fetus to clindamycin, tetracycline, chloramphenicol, metronidazole, gentamicin, and related antimicrobial agents*

Drug	Median MIC (μg/ml)	Cumulative % strains inhibited at various concn (μg/ml)							
		0.2	0.4	0.8	1.6	3.1	6.2	12.5	≥25
Clindamycin (11)[a]	0.24	36	73		91	100			
Lincomycin (11)	3.7			18	27	45	91		100
Erythromycin (11)	2.5	9			36	54	73	91	100
Tetracycline (11)	0.27	45	73	91	100				
Doxycycline (11)	0.24	45	64	91	100				
Minocycline (11)	0.12	64	82	91	100				
Chloramphenicol (11)	3.1	9		27	36	54	73	100	
Metronidazole (11)	2.4	27	45			64	73	100	
Gentamicin (10)	0.25	40	80	100					
Kanamycin (10)	2.0				40	80	100		
Amikacin (10)	0.8				100				

[a] Number of strains tested.

to ampicillin, all were inhibited by readily achievable serum concentrations of these antibiotics. All strains were highly resistant to vancomycin.

In contrast, *C. fetus* was exquisitely susceptible to the tetracyclines, gentamicin, and amikacin. All strains were inhibited by 1.6 μg of tetracycline, doxycycline, and minocycline per ml, 0.8 μg of gentamicin per ml, and 1.6 μg of amikacin per ml. All strains were also inhibited at concentrations of clindamycin, chloramphenicol, metronidazole, and kamaycin achievable in serum; but were relatively resistant to lincomycin and erythromycin.

DISCUSSION

Our data on the in vitro antimicrobial susceptibility of clinical isolates of *C. fetus* are in general agreement with those obtained with seven bacteremic isolates reported by Butzler et al. (4). Similar to our finding, all except one of their strains were resistant to penicillin and cephalothin, whereas only two of seven were resistant to ampicillin. The consistent in vitro resistance to penicillin is in keeping with frequent reports of therapeutic failure with this agent in the treatment of *C. fetus* infections (6, 13, 14). The unique susceptibility of *C. fetus* to tetracycline and gentamicin was also noted by Butzler et al. (4). This is consonant with the generally favorable response to tetracycline therapy in our own experience, as well as that of the reported English literature (13–15, 17, 21). Gentamicin has also been recommended by some as the treatment of choice for severe *C. fetus* infections (4); however, existing clinical experience with this agent is too scanty to permit adequate evaluation of its in vivo efficacy. Results of therapy with clindamycin and chloramphenicol have been variable (5, 13, 20–22). Thus, these data on the in vitro susceptibility of various agents correlated remarkably well with clinical experience of their clinical efficacy as re-

ported in the literature. It is our belief that for initial empiric therapy of *C. fetus* infections, parenteral tetracycline is the antibiotic of choice. The selection of alternative antimicrobial agents during subsequent management should be guided by in vitro testing of the organisms' drug susceptibility. Since infections with *C. fetus* are characteristically relapsing in nature, sustained antibiotic therapy for at least 3 to 4 weeks is generally recommended (2).

The in vitro activity of metronidazole against *C. fetus* is of particular interest. Fernie et al. (8) also demonstrated unique activity of dimetridazole, an analog of metronidazole, against ovine strains of *C. fetus*. Until recently, metronidazole and other nitroimidazole derivatives were considered to be active only against obligate anaerobes (19), probably by serving as specific electron acceptors for reduced ferredoxin, thus interfering with electron transfer in the phosphoroclastic reaction essential for survival of obligate anaerobes (7, 16). Our demonstration of inhibition of *C. fetus* by metronidazole suggests that alternative mechanisms of action, effective also against microaerophilic bacteria, should be explored for the antibacterial activity of metronidazole and other nitroimidazole derivatives.

LITERATURE CITED

1. **Bailey, W. R., and E. G. Scott (ed.).** 1970. Diagnostic microbiology. C. V. Mosby, St. Louis.
2. **Bokkenheuser, V.** 1970. Vibrio fetus infection in man. I. Ten new cases and some epidemiologic observations. Am. J. Epidemiol. **91**:400–409.
3. **Brown, W. J., and R. Sautter.** 1977. *Campylobacter fetus* septicemia with concurrent salpingitis. J. Clin. Microbiol. **6**:72–75.
4. **Butzler, J. P., P. Dekeyser, and T. Lafontaine.** 1974. Susceptibility of related vibrios and *Vibrio fetus* to twelve antibiotics. Antimicrob. Agents Chemother. **5**:86–89.
5. **Cooper, I. A., and S. K. Slee.** 1971. Human infection by Vibrio fetus. Med. J. Aust. **1**:1263–1267.
6. **Eden, A. N.** 1962. Vibrio fetus meningitis in a newborn infant. J. Pediatr. **61**:33–38.
7. **Edwards, D. I., M. Dye, and H. Carne.** 1973. The selective toxicity of antimicrobial nitroheterocyclic drugs. J. Gen. Microbiol. **76**:135–145.
8. **Fernie, D. S., D. A. Ware, and R. W. A. Park.** 1977. The effect of the nitroimidazole drug dimetridazole on microaerophilic campylobacters. J. Med. Microbiol. **10**:233–240.
9. **Franklin, B., and D. D. Ulmer.** 1974. Human infection with Vibrio fetus. West. J. Med. **120**:200–204.
10. **Gunderson, C. H., and G. E. Sack.** 1971. Neurology of Vibrio fetus infection. Neurology **21**:307–309.
11. **Holdeman, L. V., and W. E. C. Moore (ed.).** 1972. Anaerobe laboratory manual. Virginia Polytechnic Institute Anaerobe Laboratory, Blacksburg.
12. **Kilo, C., P. O. Hagemann, and J. Marzi.** 1965. Septic arthritis and bacteremia due to Vibrio fetus—report of an unusual case and review of the literature. Am. J. Med. **38**:962–971.
13. **King, E. O.** 1957. Human infections with Vibrio fetus and a closely related Vibrio. J. Infect. Dis. **101**:119–128.
14. **Loeb, H., J. L. Bettag, N. K. Yung, S. King, and D. Bronsky.** 1966. Vibrio fetus endocarditis—report of 2 cases. Am. Heart J. **71**:381–386.
15. **Mandel, A. D., and R. C. Ellison.** 1963. Acute dysentery syndrome caused by Vibrio fetus—report of a case. J. Am. Med. Assoc. **185**:536–538.
16. **O'Brien, R. W., and J. G. Morris.** 1972. Effect of metronidazole on hydrogen production by Clostridium acetobutylicum. Arch. Microbiol. **84**:225–233.
17. **Soonattrakul, W., B. R. Andersen, and J. H. Bryner.** 1971. Raw liver as a possible source of Vibrio fetus septicemia in man. Am. J. Med. Sci. **261**:245–249.
18. **Steers, E., E. L. Foltz, B. S. Graves, and J. Riden.** 1959. Inocula-replicating appartus for routine testing of bacterial susceptibility to antibiotics. Antibiot. Chemother. **9**:307–311.
19. **Tally, F. P., V. L. Sutter, and S. M. Finegold.** 1975. Treatment of anaerobic infections with metronidazole. Antimicrob. Agents Chemother. **7**:672–675.
20. **Targan, S. R., A. W. Chow, and L. B. Guze.** 1976. Spontaneous peritonitis of cirrhosis due to Campylobacter fetus. Gastroenterology **71**:311–313.
21. **Toala, P., A. McDonald, and E. H. Kass.** 1970. Septicemia caused by Vibrio fetus. Arch. Intern. Med. **126**:306–308.
22. **Vesely, D., D. S. MacIntyre, and K. R. Ratzan.** 1975. Bilateral deep brachial vein thrombophlebitis due to Vibrio fetus. Arch. Intern. Med. **135**:994–995.