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The Life and Times of the Enterococcus

BARBARA E. MURRAY

University of Texas Medical School at Houston, Houston, Texas 77030

cocci into four divisions: pyogenic, viridans, lactic, and enterococcus. The latter term was used for organisms that (for the most part) grew at 10 and 45°C, in 6.5% NaCl, and at

malodoratus were all distinct; that "*S. faecium* var. *mobilis*" was the same as *S. casseliflavus*; that *S. faecalis* and its former subspecies *liquefaciens* and *zymogenes* were indeed

split esculin was also noted (191). Many of these character-

chickens, designated *S. gallinarum*, were distinct from *S.*

TABLE 1. Tests used to differentiate selected gram-positive organisms[a]

Test	% Positive					
	Enterococci	Lactococci	Aerococci	Pediococci	Leuconostocs	Lactobacilli
Gas from glucose	<1	0	0	0	100	50
Vancomycin resistance[b]	<1	0	0	100	100	90
Reaction with streptococcal group D antiserum	80	0	0	95	35	25
Bile-esculin positive	99	75	60	100	90	50
PYRase positive[c]	100	69	100	0	0	7
Growth						
In 6.5% NaCl broth	100	56	100	35	60	40
At 45°C	99	25	0	83	0	60
At 10°C	85	100	0	4	75	100

[a] Adapted from Facklam et al. (67).

[b] Although still very rare, acquired resistance to vancomycin has now been described (see text).

[c] Hydrolysis of PYR.

culture plus the demonstration of their ability to hydrolyze esculin in the presence of bile and to grow in the presence of 6.5% NaCl (62, 63). However, because some enterococci may require up to 48 h of incubation for the correct reaction to occur (17) and because it is often important clinically to known quickly whether an isolate is likely to be an *Enterococcus* or a *Streptococcus* sp., more rapid screening procedures have been sought. One such system is a 2-h test that uses 0.2% esculin in a buffered 5% NaCl solution which was bile-esculin, PYR, and growth in 6.5% NaCl and at 45 and 10°C, may be necessary (Table 1). For further details, the reader is referred to recent papers by Facklam and Collins (66) and Facklam et al. (67).

Species Identification

In many instances, it may not be necessary to identify enterococci to species. For example, with urinary tract and

glycerol, whereas most *E. faecium* but not *E. faecalis* produce acid from melibiose and L-arabinose (43, 65, 66, 187). Several biochemical reactions can be suggestive of the other enterococcal species (42, 43, 66, 69). *E. casseliflavus*, for example, is motile and produces yellow pigment; *E. mundtii* produces yellow pigment and is not motile; *E. gallinarum* is motile but does not produce yellow pigment;

scheme, using both phage and enterococcines, with over 900 enterococci from two hospitals (114). A large percentage (79%) could be typed into one of 25 phage types, although 61% belonged to a single phage type. Seventy-nine percent could also be placed into one of six enterococcine groups which consisted of 85 enterococcinotypes; half belonged to one group. When phage typing was combined with entero-

the patient or with the presence of polymicrobial bacteremia (193). Nine of 14 diabetics, 6 of 10 patients with malignancy or granulocytopenia, 7 of 8 with renal failure, and 3 of 5 alcoholics died (193). In the study by Malone et al., the mortality was 44%; this study did not assess the same factors rapidly or ultimately fatal underlying disease were signifi-

the third most common cause of nosocomial UTIs, causing 14.7% in the 1984 report (36). As will be discussed further below, the hospital setting is complex and a number of factors may contribute to acquisition of enterococcal urinary infection, including frequent instrumentation, prior therapy tated patients, and transmission of resistant organisms.

children and adults. Most cases seem to be related to an underlying disorder. In a 1961 review, 12 of 294 cases of meningitis appeared to be caused by enterococci; many of these patients were said to have had a long-term primary

or prior antibiotic therapy or all three (56).

always stated that anaerobic cultures were performed. Enterococci have also caused acute salpingitis, peripartum maternal infection (such as endometritis) with bacteremia, and abscess formation following Cesarean section (83, 122,

gynecological patients, 18 (13%) were due to enterococci,

The use of antimicrobial agents lacking enterococcal activity has been implicated as an important factor in the development of enterococcal superinfection (16, 46, 74, 98, 137, 176, 207, 230). Moellering reviewed 2,107 patients treated with moxalactam and found that 2.1% developed an enterococcal superinfection during or shortly after moxalactam therapy (127). This infection occurred in 28 (6.6%) of 572 patients who had a UTI; of note, 28 of these 38 had urinary

environment in which antimicrobial agents are heavily used; the hospital setting provides the antibiotics which eliminate or suppress susceptible bacteria, thereby providing a selective advantage for resistant organisms, and the hospital also provides the potential for dissemination of resistant enterococci via the usual routes of nosocomial spread.

Antimicrobial resistance can be divided into two general types, that which is an inherent or intrinsic property and that

ampicillin, and other penicillins in broth macrodilution systems are typically >100 μg/ml (7, 113, 139).

A notable weakness of cephalosporins is that none of these agents routinely inhibits enterococci sufficiently to warrant its clinical use. MICs of cephalothin range from 6.3 higher (72, 113, 158, 209, 218). Although the in vitro activity

agar (91). When enterococcal strains were tested in urine, the mean MIC increased 60-fold; this effect was reversed by methotrexate (235). In addition to the problems with MIC determination, there are also conflicting reports as to whether or not TMP/SMX is bactericidal against enterococci indicate efficacy in vivo, TMP/SMX should not be consid-

because its rate of transposition is increased by exposure to low levels of erythromycin (211).

of enterococci have been resistant to tetracycline (1, 6). Several different genes have been found, including *tetL* (which is contained in the well-studied plasmid pAMα1) and

tobramycin, but not to streptomycin (100). In 1983, several reports, including two from my laboratory, documented

gentamicin and to all aminoglycosides, including gentamicin and streptomycin. In these studies, which included strains

from Houston, Tex., Bangkok, Thailand, and Santiago

abstr. no. 1121, 1989). Working with Jan Patterson, we have of 39.5 kilodaltons (223b). Although it is postulated that this

and found that, although the restriction endonuclease diges- Ala-D-Ala, the mechanism is not yet understood. One of the

tion patterns are different, there is extensive homology vancomycin resistance genes has been cloned, and a probe

between most of these plasmids (149; Patterson et al., 28th from this strain hybridizes only with enterococci with high-

patients for whom an extracardiac source cannot be identified, particularly when the enterococcus is present in pure culture and was community acquired (129). Whether or not these lengthy regimens are truly necessary or whether shorter courses or single-drug therapy will suffice is not known.

Endocarditis. Therapy of enterococcal endocarditis has patients and animals with enterococcal endocarditis are also cured by penicillin alone, these results are not surprising. Again, however, care must be taken with generalizations, since failures of ampicillin to cure endocarditis in patients infected with a strain of *E. faecalis* resistant to multiple aminoglycosides have been reported (76, 108). It should also be reiterated that, in the absence of HLR, ampicillin plus an

mend testing for beta-lactamase since the organism may

appear susceptible by routine methods although such isolates

that many laboratories routinely use for other organisms

TABLE 2. Zone of inhibition around antibiotic disks

Antibiotic	Strains	Strains	Medium[c]	Reference

strains and Mueller-Hinton agar plus blood, the lower-content disks gave zones of 6 mm for streptomycin, gentamicin, and kanamycin and 6 to 10 mm for tobramycin; on Mueller-Hinton agar without blood, the zones were 6 to 7 mm for all four agents. On Mueller-Hinton agar plus blood, synergy-susceptible strains had zones of ≥14 mm for streptomycin and ≥20 mm for gentamicin, tobramycin, and kanamycin; on Mueller-Hinton agar without blood, zones

discrepant strains were not reported (198). The disk method and the in-house broth microdilution method also detected three of three streptomycin-resistant *E. faecium* strains; none of seven *E. faecium* strains had HLR to gentamicin.

Recommendations for Screening for HLR to Aminoglycosides

tobramycin, and ≥10 mm for kanamycin (Table 2). The

method currently appear highly reliable for detecting *E.*

secondary invaders. Since nosocomial isolates of entero-

cocci have displayed resistance to essentially every useful

20. **Bridge, P. D., and P. H. A. Sneath.** 1982. *Streptococcus gallinarum* sp. nov. and *Streptococcus oralis* sp. nov. Int. J.

Microbiology, Washington, D.C.

42. **Collins, M. D., J. A. E. Farrow, and D. Jones.** 1986. *Enterococcus mundtii* sp. nov. Int. J. Syst. Bacteriol. **36**:8–12.

43. **Collins, M. D., D. Jones, and J. A. E. Farrow, R. Kilpper-Bälz, and K. H. Schleifer.** 1984. *Enterococcus avium* nom. rev., comb. nov.; *E. casseliflavus* nom. rev., comb. nov.; *E. durans* nom. rev., comb. nov.; *E. gallinarum* comb. nov.; and *E. malodoratus* sp. nov. Int. J. Syst. Bacteriol. **34**:220–223.

44. **Combes, T., C. Carlier, and P. Courvalin.** 1983. Aminoglycoside-modifying enzyme content of a multiply resistant strain of *Streptococcus faecalis*. J. Antimicrob. Chemother. **11**:41–47.

45. **Conn, J. H., J. D. Hardy, C. M. Chavez, and W. R. Fain.** 1970. Infected arterial grafts: experience in 22 cases with emphasis on unusual bacteria and technics. Ann. Surg. **171**:704–714.

46. **Coudron, P. E., C. G. Mayhall, R. R. Facklam, A. C. Spadora, V. A. Lamb, M. R. Lybrand, and H. P. Dalton.** 1984. *Strepto-*

(ed.), Manual of clinical microbiology, 3rd ed. American Society for Microbiology, Washington, D.C.

64. **Facklam, R., G. S. Bosley, D. Rhoden, A. R. Franklin, N. Weaver, and R. Schulman.** 1985. Comparative evaluation of the API 20S and AutoMicrobic Gram-Positive Identification systems for non-beta-hemolytic streptococci and aerococci. J. Clin. Microbiol. **21**:535–541.

65. **Facklam, R. R., and R. B. Carey.** 1985. Streptococci and aerococci, p. 154–175. *In* E. H. Lennette, A. Balows, W. J. Hausler, Jr., and H. J. Shadomy (ed.), Manual of clinical microbiology, 4th ed. American Society for Microbiology, Washington, D.C.

66. **Facklam, R. R., and M. D. Collins.** 1989. Identification of *Enterococcus* species isolated from human infections by a conventional test scheme. J. Clin. Microbiol. **27**:731–734.

67. **Facklam, R. R., D. Hollis, and M. D. Collins.** 1989. Identifica-

83. **Gibbs, R. W., H. M. Listwa, and R. B. Dreskin.** 1977. A pure

tance to multiple aminocyclitol aminoglycosides. Diagn. Mi-

19:17–20.

104. **Ingerman, M., P. G. Pitsakis, A. Rosenberg, M. T. Hessen, E.**

84. **Glew, R. H., and R. C. Moellering, Jr.** 1979. Effect of protein

Abrutyn, B. E. Murray, and M. E. Levison. 1987. β-Lactamase

binding on the activity of penicillins in combination with

production in experimental endocarditis due to aminoglyco-

gentamicin against enterococci. Antimicrob. Agents Chemo-

side-resistant *Streptococcus faecalis*. J. Infect. Dis. **155**:1226–

ther. **15**:87–92.

1232.

85. **Goodhart, G. L.** 1984. In vivo v in vitro susceptibility of

105. **Jorgensen, J. H., S. A. Crawford, and G. A. Alexander.** 1983.

term peritoneal dialysis before and after human cadaveric renal transplantation. J. Clin. Pathol. **22**:539–544.

124. **Lemoine, L., and P. R. Hunter.** 1987. Enterococcal urinary tract infections in a teaching hospital. Eur. J. Clin. Microbiol. **6**:573–574.

125. **Loewe, L., S. Candel, and H. B. Eiber.** 1951. Therapy of Ann. Intern. Med. **34**:717–736.

144. **Moellering, R. C., Jr., C. Wennersten, and T. Medrek.** 1971. Prevalence of high-level resistance to aminoglycosides in clinical isolates of enterococci, p. 335–340. Antimicrob. Agents Chemother. 1970.

145. **Moellering, R. C., Jr., C. Wennersten, and A. J. Weinstein.** 1973. Penicillin-tobramycin synergism against enterococci: a Agents Chemother. **3**:526–529.

imental intra-abdominal abscess. Infect. Immun. 13:22–26. therapy of bacterial endocarditis. Ann. Intern. Med. 92:390–395.

163. **Orla-Jensen, S.** 1919. The lactic acid bacteria. Mem. Acad. R. Soc. Danemark Sect. Sci. Ser. 8 **5**:81–197.

183. **Schaberg, D. R., and M. J. Zervos.** 1986. Intergeneric and

204. **Thadepalli, H., A. K. Mandal, K. Rambhatla, and V. T. Bach.** 1981. Is penicillin alone effective in enterococcal endocarditis? An experimental study in rabbits. Chemotherapy (Basel) **27:**

205. **Thauvin, C., G. M. Eliopoulos, S. Willey, C. Wennersten, and R. C. Moellering, Jr.** 1987. Continuous-infusion ampicillin therapy of enterococcal endocarditis in rats. Antimicrob. Agents Chemother. **31:**139–143.

223a. **Willey, S. H., R. G. Hindes, G. M. Eliopoulos, and R. C. Moellering, Jr.** 1989. Effects of clindamycin-gentamicin and other antimicrobial combinations against enterococci in an Obstet. **169:**199–202.

223b. **Williamson, R., S. Al-Obeid, J. H. Shlaes, F. W. Goldstein, and D. M. Shlaes.** 1989. Inducible resistance to vancomycin in *Enterococcus faecium* D366. J. Infect. Dis. **159:**1095–1104.