Treatment of coagulase-negative staphylococcal infections: dilemmas for laboratory and clinician

The proliferation of publications on coagulase-negative staphylococcal infections would lead us to believe that this group of pathogens is the nosocomial counterpart of the Black Death: epidemic, virulent and virtually untreatable. It should be remembered that this picture of dramatically rising incidence and high mortality emanates from tertiary care institutions (Ponce de Leon & Wenzel, 1984). Data on coagulase-negative staphylococcal sepsicaemia from a community hospital setting indicated only half the incidence and no upward trend (Righter, 1987); the overwhelming majority of patients are in this type of setting. Even when it has been decided (after careful thought) that a culture represents a pathogen, not all of these infections require antimicrobial therapy. Simple removal of foreign bodies that form foci of infection, such as vascular access devices, cures many (Davies & Stone, 1986).

The ability to produce slime is a virulence factor but disappoints us as a means of distinguishing pathogens from commensals. However, the information may be valuable when we are attempting to cure an infection associated with a foreign body left in situ, since this long shot is even less likely to succeed with a slime producer (Davenport et al., 1986; Kristinsson, Spencer & Brown, 1986). Yet even less interest is shown by diagnostic laboratories in this test than in speciation.

More problems face the clinician and laboratory director when they have decided to proceed with specific therapy. Vancomycin shows excellent activity and has been proven in the clinical situation (Lowy & Hammer, 1983). Both penicillin and cloxacillin are appropriate for susceptible isolates, but resistance rates are high (Fass et al., 1986). With Staphylococcus aureus, resistance to methicillin, cloxacillin, and nafcillin are synonymous; in contrast, with coagulase-negative staphylococci, differing results may be obtained (Coudron et al., 1986; Fass et al. 1986). Direct plating of a large inoculum on to agar containing methicillin yields the highest resistance rates (Karchmer, Archer & Dismukes, 1983; Coudron et al., 1986) but are these results clinically relevant? This test is far from standardized, with various concentrations of methicillin (12.5–100 mg/l) and incubation periods (up to 72 h) recommended. Modified Kirby-Bauer disc diffusion as recommended by the National Committee for Clinical Laboratory Standards (1984) misses some strains resistant by quantitative methods (Coudron et al., 1986; Fass et al., 1986). A change in the oxacillin disc content has been proposed (McDougal & Thornsberry, 1984). Appropriate breakpoint concentrations for dilution methods are also undecided. Cation supplementation alters results (Woods et al., 1986). The use of 2% to 5% sodium chloride supplementation and the incubation temperature lowered to 30°C have been studied, but both are unphysiological and therefore rejected by some. Incubation for 48 h increases resistance rates but differs radically from the clinical situation.

The heteroresistance phenomenon occurs with all staphylococci. For S. aureus, its clinical implication is known: even though cephalosporin resistance may be present in only a minority of the population of methicillin-resistant organisms, these infections respond poorly to cephalosporins and therefore laboratories must routinely report such isolates as resistant to all β-lactam drugs. The same policy is strongly recommended for coagulase-negative staphylococci (Lowy & Hammer, 1983; Davies & Stone, 1986), but the appropriateness of this is questionable. The direct consequence of such reporting policy would be many more therapeutic courses of vancomycin. Overall, the morbidity and mortality from coagulase-negative staphylococcal infections is far lower than from S. aureus. Furthermore, much over-reporting is inevitable; only 22% of routine isolates may be significant (Sewell et al., 1982). A report of 'resistant' from a diagnostic laboratory is rarely questioned or contravened. Is it responsible on the part of laboratories to prompt therapy in all of these cases with vancomycin, a toxic and expensive agent? Laboratory
reporting policies should certainly reach beyond in-vitro accuracy to protect patients whenever possible from ineffective therapy. In the case of *S. aureus*, clinical data have given them clear direction.

With coagulase-negative staphylococci, cephalosporin-resistant subpopulations are detectable in methicillin-resistant strains, but the proportion of resistant organisms is lower than with *S. aureus* (Archer, 1978). However, cephalexin, cefazolin and cefamandole have been reported to have bactericidal activity against some nafcillin resistant organisms (Mordenti et al., 1986). Data from experimental infections discourage cephalosporin use: in experimental endocarditis in rabbits caused by methicillin-resistant isolates, nafcillin, cefalothin and cefamandole were equally ineffective (Vazquez & Archer, 1980; Lowy, Wexler & Steigbigel, 1982). The experimental endocarditis model, however, is a more rigorous test than most clinical situations.

Few clinical treatment failures with cephalosporins have been reported. In three such cases, the patients were neutropenic (Wade et al., 1982; Hutton et al., 1985). In a study of patients with prosthetic valve endocarditis, only two actually received single drug treatment without surgery, one with vancomycin, the other with a β-lactam, and both treatments failed (Karchmer et al., 1983). In contrast, good response rates to cefazolin have been reported in patients receiving immunosuppressive therapy; in fact, cefazolin cured four of five septicemias associated with Hickman-type catheters without line removal, but it is uncertain how many of these were methicillin-resistant (Winston et al., 1983). Three of five patients receiving continuous ambulatory peritoneal dialysis, who developed methicillin resistant coagulase-negative staphylococcal peritonitis responded clinically to intraperitoneal cephalexin (Baddour et al., 1986). In a recent report, five patients with methicillin-resistant septicemias were successfully treated with cephalosporins (Righter, 1987). One wonders whether cephalosporin resistant subpopulations, if only present in such small numbers that they evade detection by routine susceptibility testing methods, perhaps persist to cause treatment failure only in certain circumstances favouring the pathogen. This may reflect the lower intrinsic virulence of coagulase-negative staphylococci than of *S. aureus*.

Cefamandole is the most active β-lactam in vitro against coagulase-negative staphylococci. In contrast to the poor results in experimental infections, the clinical outcome has been good (Frongillo et al., 1986).

Some options have not been studied in human infections. Amikacin and netilmicin are the most active aminoglycosides in vitro (Davies et al., 1986; Gil, Selepak & Williams, 1983). The combination of gentamicin plus vancomycin was the most effective regimen in the experimental endocarditis model (Lowy et al., 1979). Rifampcin and fusidic acid are synergistic in vitro (Farber, Yee & Karchmer, 1986).

The availability of a non-toxic drug with a therapeutic activity similar to that of vancomycin would simplify matters greatly both in the laboratory and at the bedside. Teicoplanin offers promise. Administration is easier and early studies suggest lower risk of toxicity (Bibler et al., 1987). In vitro, teicoplanin is twice as active as vancomycin against staphylococci (Neu & Labthavikul, 1983) but concern exists over the wider range of susceptibility (up to 32 mg/l) than with vancomycin (up to 8 mg/l) (Arioli & Pallanza, 1987). Early clinical results are conflicting: all three patients were cured in one report (Bibler et al., 1987) but two of four failed in another (Glupczynski et al., 1986).

It is premature to report all methicillin-resistant coagulase-negative staphylococci as resistant to cephalosporins. Clinicians treating these infections must learn to decide which laboratory reports confirm the diagnosis, which of these require antimicrobial therapy, and which drug is appropriate. Vancomycin is clearly not necessary in all cases; however, it is presently the drug of choice when the infection occurs in a setting of profound neutropenia, and when one is attempting to cure an infection without removing a prosthetic device.

The difference in case mix between community and university hospitals results in very different patterns of nosocomial infection. Great harm is possible when recommendations derived from studies on certain patient populations are generalized without critical evaluation. Laboratory reporting policies shape prescribing patterns; laboratory directors must shoulder the responsibility of interpreting the evidence and tailoring their policies to facilitate optimal treatment of patients.

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References


Selective decontamination

Selective decontamination is a technique for prevention of colonization and infection in high risk patients. This is achieved by elimination of aerobic, potentially pathogenic, microorganisms from throat and intestine whilst preserving the indigenous, mostly anaerobic flora. This method is based on three observations, as follows. 1. There are major differences between microorganisms depending on their intrinsic pathogenic potential (Kurrle et al., 1981). Three groups can be distinguished: indigenous (mostly anaerobic) flora that lives in symbiotic relationship with the host and has a low pathogenic potential; aerobic microorganisms that cause community-acquired infections; and aerobic bacteria involved in hospital-acquired infections. 2. The indigenous flora is rarely involved in infections and has important physiological functions (Mackowiak, 1982), contributing to defence against aerobic colonization (Buck & Cooke, 1969). 3. Colonization and infection of the respiratory and urinary tracts and wounds generally occur after a previous stage of oropharyngeal and/or gastrointestinal colonization by identical aerobes (van Saene et al., 1986). Crucial to the understanding of the genesis of infections is that infections caused by microorganisms acquired in the hospital ("exogenous" Enterobacteriaceae, Pseudomonadaceae and Acinetobacter spp.) are in fact endogenous, because multiplication in the throat and/or the intestine forms an essential stage in the development of nosocomial colonization and infection. Combining successful elimination of aerobic potentially pathogenic microorganisms from throat and intestine with preservation of indigenous flora is probably a contradiction in terms, for two reasons. Destruction of aerobes lowers the rate of molecular oxygen consumption permitting an increase in the pO$_2$ of the lumen contents from 5 to 60 mm Hg; under such conditions strictly anaerobic microorganisms can no longer survive, even though they may not themselves be sensitive to the antimicrobial agents used (Poth, 1982). Secondly, elimination of aerobes from throat and intestine generally requires much higher concentrations of antimicrobials so that agents that are only active against aerobes in systemic concentrations may become active against the indigenous flora as well when "topical" doses are used (King, 1980). 'Selective' should be interpreted as 'as selective as possible', the efficacy of complete aerobic elimination being more important than complete selectivity.

Many regimens have been tried, three of which turned out to have some value for suppression of intestinal flora: nonabsorbable gentamicin, vancomycin and nystatin (GVN); framycetin (neomycin), colistin (polymyxin E) and nystatin (FRACON); and absorbable trimethoprim-sulphamethoxazole combined with nonabsorbable polymyxin E and amphotericin B (SXTAPM). A series of studies has shown that the application of these oral regimens significantly reduces the incidence of infections, but not of febrile episodes (Schimpff et al., 1975; Storrng et al., 1977; Rozenberg-Arska, Dekker & Verhoef, 1983). However, from the microbiological point of view intestinal colonization rates remained high, revealing an incomplete flora elimination; microorganisms both sensitive and resistant were colonizing the intestine during flora suppression (Klasterly et al., 1974; Kurrle et al., 1986). Microbiologically active faecal concentrations were apparently subinhibitory or were not obtained at all. Theoretically, three conditions may occur in the intestine under oral antibiotic regimens. Higher concentrations result in complete elimination, emergence of resistance being rare in the absence of potentially pathogenic aerobes. Following fluctuating concentrations the elimination is incomplete, and these circumstances promote emergence of resistance. If faecal microbiologically active concentrations are not obtained neither elimination nor resistance can occur. Emergence of resistance by one or more of three mechanisms: genetic change, acquisition of new resistant strains or overgrowth of resistant strains from very small numbers already

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