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Gram-positive bacteria: spread and antimicrobial resistance in university and community hospitals in the USA

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Gram-positive bacteria have become more important as a source of both community and nosocomial infection in the United States during the past few years. In part, this has been due to the increasing prevalence of resistance of some of these organisms to commonly-employed antimicrobials. Initially, such resistance was seen primarily in university and referral hospitals. Spread of resistant strains to the community hospital recently has become prominent for many of these organisms. Exemplifying these trends are methicillin-resistance in *Staphylococcus aureus*, vancomycin-resistance in coagulase-negative staphylococci, relative resistance to penicillin among pneumococci, aminoglycoside-resistance in viridans streptococci, and resistance to both β-lactams and aminoglycosides in enterococci. These developments highlight the importance of the Gram-positive cocci in today's clinical practice in the USA. The need to define and deal with these trends is emphasized by the speed with which the changes have developed in both university and community hospitals.

Introduction

During the early 1980s, major changes occurred in the United States of America in the occurrence and aetiology of severe infections, such as bacteraemia (McGowan, 1985). Among the most important of these was the resurgence of Gram-positive cocci as causes of severe infection. Much of this increase was closely associated with development of antimicrobial resistance in several genera, and spread of resistant strains to new segments of the population. This review will consider several changes in rates of occurrence and in patterns of resistance among the Gram-positive cocci that have been of particular clinical impact.

Increasing occurence of Gram-positive coccal infections

The dramatic increase in impact of these organisms is shown by data on occurrence of hospital-associated bacteraemia at Grady Memorial Hospital, Atlanta, Georgia, in 1983 compared with 1975 (Figure 1). Compared with their contribution in 1975, Gram-positive cocci increased their role dramatically in 1983 (McGowan, 1986). By contrast, the relative proportion of cases due to Gram-negative aerobic bacilli decreased somewhat in 1983 compared with the earlier year.

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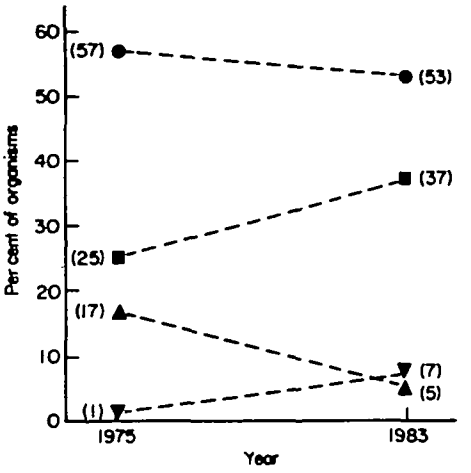

Figure 1. Increasing importance of Gram-positive cocci as source of nosocomial bloodstream invasion, 1975 (six months) and 1983 (six months), Grady Memorial Hospital, Atlanta, Georgia. Data points between 1975 and 1983 are represented by a broken line, and do not depict actual values. (From McGowan, 1986, with permission of the publisher.) ●, Gram-negative aerobic bacilli; ■, Gram-positive cocci; ▲, anaerobes; ▼, fungi.

A national surveillance programme for hospital infection conducted by the Centers for Disease Control also shows the same trend. This programme, the National Nosocomial Infections Study (NNIS), included information from approximately 50 hospitals for the year 1984, the latest year for which data have been published (Horan *et al.*, 1986) (Figure 2). Three groups of Gram-positive cocci, *Staphylococcus aureus*, *Staph. epidermidis*, and Group D streptococci, accounted for 34% of all bloodstream pathogens in that year. The contribution of other Gram-positive cocci was not specifically reported, but would have increased the relative impact of these bacteria.

At Grady Memorial Hospital during a three-month surveillance period in 1984, Gram-positive cocci and rods accounted for half the isolates from bacteraemia cases

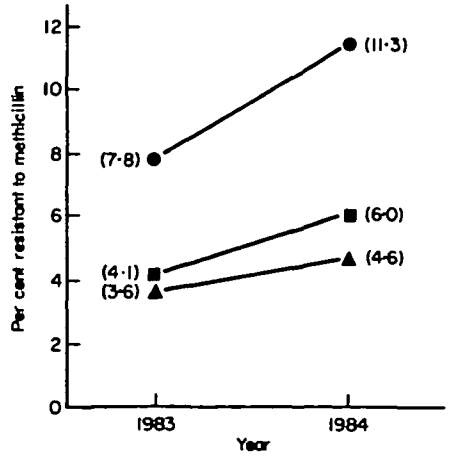

Figure 2. Prevalence of methicillin-resistance in *Staph. aureus* in nosocomial infections, by hospital category, National Nosocomial Infections Survey, 1983 and 1984. (From McGowan, 1986, with permission of the publisher.) ●, Large teaching hospitals; ■, non-teaching hospitals; ▲, small teaching hospitals.

Table I. Bacteraemic infections by organism group and age group, Grady Memorial Hospital, Atlanta, Georgia, July–September 1984

Organism group	Age group (years) <30	30–59	60+
Gram-positive cocci and rods	46 (50%)	24 (31%)	25 (24%)
Gram-negative aerobic bacilli	27 (29%)	45 (59%)	56 (55%)
Anaerobes	11 (12%)	4 (5%)	19 (18%)
Fungi	8 (9%)	4 (5%)	3 (3%)
Totals	92 (100%)	77 (100%)	103 (100%)

among patients less than 30 years of age, for about one-third of cases in the age group 30–59 years, and about one-quarter of those in patients 60 years and older (Table I).

The impact of these organisms has been even greater in oncology centres in the United States (Robinson, Tegtmeier & Zaia, 1984). Compared with the distribution in a general hospital like Grady Memorial Hospital, the relative proportion of cases associated with Gram-positive cocci at one oncology centre was almost 10% higher, and the overall attack rate of nosocomial bacteraemia was four times higher (Table II).

Gram-positive pathogens have also become a frequent source of infection in patients with Acquired Immune Deficiency Syndrome (AIDS) and other manifestations of HIV infection. Gram-positive cocci were recovered in 24 (71%) of 34 episodes of bacteraemia among patients with AIDS or Aids-Related Complex (ARC) studied in Boston (Witt, Craven & McCabe, 1987).

Changes in infection patterns for selected organisms

Staphylococcus aureus

The increasing frequency of *Staph. aureus* infections in the United States paralleled a marked increase in the presence of strains resistant to methicillin and similar drugs.

Table II. Nosocomial bacteraemia—relative impact of organism groups in a cancer centre and a general hospital in the USA

	Hospital type Oncology centre[a]	General hospital[b]
Overall attack rate	2·2%	0·5%
Per cent of cases due to:		
Gram-positive cocci	40%	31%
Gram-negative aerobic bacilli	38%	55%
Anaerobes	10%	10%
Fungi	13%	4%

[a]City of Hope National Medical Center, Duarte, California, USA, 1978–1981 (Robinson *et al.*, 1984).

[b]Grady Memorial Hospital, Atlanta, Georgia, USA, 1975 and 1983 (McGowan, 1985).

Table III. Susceptibility to methicillin among strains of *Staph. aureus* isolated from blood culture, by type of infection, Grady Memorial Hospital, 1983–1986

	Type of infection			
	Community-acquired		Nosocomial	
Year	Total isolates	Per cent susceptible	Total isolates	Per cent susceptible
1983	41	93%	49	71%
1984	43	88%	46	72%
1985	62	92%	44	66%
1986	89	90%	49	57%

Methicillin-resistant *Staph. aureus* (MRSA) was well entrenched in larger, university-affiliated hospitals early in the decade (Haley *et al.*, 1982). By contrast, MRSA appeared to be relatively infrequent in other settings (Atkinson & Lorian, 1984). Resistant strains have now spread to community hospitals as well. This is illustrated by data from the NNIS survey; prevalence of methicillin-resistant *Staph. aureus* strains increased by almost 50% between 1983 and 1984. The increase was seen in all types of hospitals; methicillin-resistant organisms accounted for more than 10% of *Staph. aureus* strains isolated in large teaching hospitals, 6% in non-teaching hospitals, and 4·6% in small teaching hospitals (Horan *et al.*, 1986). Similarly, a survey of 137 Veterans Administration hospitals throughout the United States showed presence of MRSA in three of the centres in 1975 and in 111 in 1984 (Preheim, Rimland & Bittner, 1987). The increase was widespread throughout the country, and occurred in hospitals of all sizes. There was no difference in the rate of increase of MRSA in hospitals of varying sizes. Veterans Administration hospitals in general have a high incidence of nosocomial infections compared with those in the community category (Standiford, 1987). At Grady Memorial Hospital (Atlanta, Georgia) from 1983–1986, the proportion of MRSA strains in community-acquired cases of bacteraemia has remained fairly constant, while the proportion of MRSA continues to increase among nosocomial cases (Table III). The number of cases of community-acquired infection with *Staph. aureus* increased in the last two years shown, while the overall occurrence of nosocomial cases remained fairly constant.

Coagulase-negative staphylococci

The frequency with which coagulase-negative staphylococci are recognized as major bloodstream pathogens in the USA continues to increase. This is especially true for nosocomial cases (Stillman, Wenzel & Donowitz, 1987). As was seen for *Staph. aureus*, coagulase-negative staphylococci are now being recognized in community hospitals as well as in the university/referral setting (Morrison *et al.*, 1986).

A recent development of concern is the recognition of vancomycin resistance in a strain of *Staph. haemolyticus* isolated from culture of peritoneal fluid. The patient had received prior therapy with vancomycin and rifampicin (Schwalbe, Stapleton & Gilligan, 1987). Resistance to vancomycin is of special importance in view of the speed with which methicillin-resistant strains of these organisms emerge after even brief courses of cephalosporin in perioperative prophylaxis in vascular and cardiac surgery

(Maki & Stevens, 1984). In addition, it has been shown quite clearly that coagulase-negative staphylococci may serve as the reservoir for transfer of resistance to *Staph. aureus* (Lyon & Skurray, 1987). It is likely that this reservoir of resistance determinants is quite extensive, in view of the redundancy with which pertinent transposons have been found in some of these strains (Thakker-Varia *et al.*, 1987).

Pneumococci

Pneumococcal infection continues to occur, but no clear increase in frequency seems apparent; the varying use and effectiveness of immunization programmes against this agent confounds analysis of trends in occurrence. A recent nationwide survey of more than 3000 strains, conducted by the Centers for Disease Control, suggested a low but appreciable level of strains demonstrating relative resistance to penicillin, and one strain with absolute resistance (Leading Article, 1987). To date, physicians in the United States have not encountered the large increase in frequency of penicillin-resistant strains of pneumococci seen in Spain and elsewhere (Pallares *et al.*, 1987).

Viridans streptococci

It is unclear whether cases of viridans streptococcal infection have increased in the United States, as the improving ability of clinical laboratories to recover the organism or an increased appreciation of its role in infections confounds the analysis. Strains of viridans streptococci highly resistant to aminoglycosides have been studied in the US, but the strains were obtained from Africa (Farber & Yee, 1987). The clinical importance of aminoglycoside resistance in these organisms remains under intense study.

Enterococci

A major development of concern in the United States is the increasing role of enterococci in nosocomial infection. Enterococci were the third most frequent source of nosocomial urinary tract infection and the sixth most frequent organisms in nosocomial bacteraemia in the NNIS study in 1984 (Horan *et al.*, 1986). At Grady Memorial Hospital, a rise in enterococcal bacteraemia was noted between 1975 and 1983 (McGowan, 1985). The rate of nosocomial bacteriuria rose sharply in approximately the same period at a university hospital (Morrison & Wenzel, 1986). The rise in occurrence of cases between the mid-1970s and mid-1980s has occurred in both university and community hospitals (Klimek *et al.*, 1980; Hoffmann & Moellering, 1987). At the same time, it remains unclear whether isolates of this organism from the respiratory tract have clinical importance (Klimek *et al.*, 1980).

Resistant enterococci have been encountered in the period as well. Strains highly resistant to aminoglycosides have been isolated in several separate regions of the United States, just as they have been noted in other areas of the world (Hoffmann & Moellering, 1987). β-Lactamase production has been demonstrated more than once in *Streptococcus faecalis* (Murray *et al.*, 1986); at least two different plasmids have been implicated and demonstrated to be transferrable. The biological significance of such resistant strains has now been confirmed in an animal model of endocarditis (Ingerman *et al.*, 1987). At some centres, aminoglycoside-resistant enterococci are a major

nosocomial hazard, and choice of effective therapy has become a problem of clinical importance (Zervos *et al.*, 1986).

Enterococcal colonization appears to be enhanced by use of the newer β-lactam drugs for prolonged periods (Jones & Thornsberry, 1985). The resistant strains have appeared most often in areas where antimicrobial use is high, such as that of intensive care (Zervos *et al.*, 1987). Plasmid-mediated mechanisms of transfer have been described, and it has been documented that exogenous transfer of resistance to other enterococcal strains can occur (Zervos *et al.*, 1987). Transfer of resistance from the enterococcus to other species of streptococcus that to date have remained susceptible to classic drugs (e.g., group A streptococcus and penicillin) has not been demonstrated, but is at least theoretically possible. These worrying observations emphasize the potential for enterococci to become increasingly important in both university and community hospitals.

Discussion

The complexity of the relationship between Gram-positive cocci and infection has recently been emphasized by new data about microbial mechanisms for transfer of resistance. Further information on ways that resistant organisms spread within the hospital setting has also emerged in the past few years (McGowan, 1987). Not only are resistance determinants transferred from species to species, but transfer from one genus to another seems more common in Gram-positive organisms than previously thought (Hoffmann & Moellering, 1987; Lyon & Skurray, 1987; Thacker-Varria *et al.*, 1987). Such a relationship appears important in recent emergence of resistance in several Gram-positive cocci. These features imply that antibiotic effects on both Gram-positive pathogens and endogenous flora must be considered in assessing the impact of drug use (Levy, Burke & Wallace, 1987).

Each of these developments emphasizes the importance of the Gram-positive cocci in today's clinical practice in the USA. The need to define and deal with these trends is emphasized by the speed with which the changes have developed in university and community hospitals, alike.

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