fibrosis are of great interest, showing that intermittent dosing of aminoglycosides, causing infrequent relatively high serum concentrations, may be less toxic than and equally efficacious as frequent dosing.

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References


Antimicrobial Resistance in Branhamella catarrhalis

Until the 1970s Branhamella catarrhalis was considered a harmless commensal of the upper respiratory tract causing isolated cases of meningitis, endocarditis and septicaemia (Kallings, 1986). Recent studies, however, have demonstrated a marked increase in the occurrence of B. catarrhalis in middle-ear exudates of children with acute otitis media (Kovatch, Wald & Michaels, 1983; Shurin et al., 1983) and respiratory secretions from predominantly elderly patients with infection secondary to underlying pulmonary disease (Ninane, Joly & Kraytman, 1978; McLeod et al., 1983; Slevin, Aitken & Thomley, 1984). In these reports were suggestions that B. catarrhalis has become more virulent; however, specific virulence factors, such as IgA protease, have not been identified (Mulks et al., 1983; Plaut, 1978; Van Hare et al., 1987).

It is difficult to tell whether the increase in incidence of B. catarrhalis infections is real. In several investigations there have been minimal changes in isolation rate during three to four year study periods, and this suggests increased awareness rather than increased incidence (Davies & Maesen, 1986; DiGiovanni et al., 1987), although comparable data from periods predating these studies would be required to clarify this point. An important factor may be the recent emphasis on the ability of diagnostic laboratories to identify B. catarrhalis correctly (Doern & Morse, 1980), and to distinguish it from non-fermentative 'non-pathogenic' Neisseria spp. such as N. cinerea and N. flavescens (Knapp et al., 1984; Vedros,
clavulanic acid with amoxycillin has been (Kallings, 1986), while the combination of erythromycin and, in adults, tetracycline (Burman, 1986). Suitable alternatives include B. catarrhalis because co-trimoxazole is efficacious for respiratory tract infections due to that co-trimoxazole is achieved. Certainly in-vivo experience suggests that co-trimoxazole is efficacious for respiratory tract infections due to that co-trimoxazole is achieved. Certainly in-vivo experience suggests that co-trimoxazole is efficacious for respiratory tract infections due to that co-trimoxazole is achieved. Certainly in-vivo experience suggests that co-trimoxazole is efficacious for respiratory tract infections due to that co-trimoxazole is achieved.

There has been a rapid increase in the rate of isolation of β-lactamase-producing strains of B. catarrhalis. Early studies showed the majority of strains to be highly susceptible to penicillin (Barber & Waterworth, 1962; Kamme, 1970). In 1977 several publications focused attention on the ability of B. catarrhalis to inactivate penicillins (Malmvall, Brorson & Johnson, 1977; Percival et al., 1977) and since then β-lactamase production in these organisms has been reported with increasing frequency (Doern et al., 1980; Kovatch et al., 1983; Ahmad et al., 1984). In our laboratory, at the end of 1982, 36% of B. catarrhalis isolates were β-lactamase producers, while by the end of 1984 the incidence had increased to 90%. All strains remained uniformly susceptible to tetracycline and resistant to trimethoprim, while susceptibility to erythromycin, sulphamethoxazole and co-trimoxazole varied slightly (DiGiovanni et al., 1987), in agreement with earlier findings of Doern et al. (1980), Brorson, Axelson & Holm (1983) and Stobberingh, Davies & Van Boven (1984). We recently examined the susceptibility of B. catarrhalis to sulphamethoxazole, trimethoprim and co-trimoxazole in some detail (Riley, DiGiovanni & Hoyne, 1987). The optimum ratio of sulphamethoxazole to trimethoprim for synergy was either 1 : 1 or 1 : 2, although the commercially available 20 : 1 ratio was still effective in vitro. Although the penetration into respiratory secretions of both components of co-trimoxazole is not good, and subinhibitory concentrations can occur, a suitable ratio for synergy may still be achieved. Certainly in-vivo experience suggests that co-trimoxazole is efficacious for respiratory tract infections due to B. catarrhalis (Burman, 1986). Suitable alternatives include erythromycin and, in adults, tetracycline (Kallings, 1986), while the combination of clavulanic acid with amoxycillin has been shown to be effective (Wallace et al., 1985; Van Hare et al., 1986).

β-Lactamase inhibitors such as clavulanic acid may be important when B. catarrhalis is acting as an indirect pathogen. In some studies isolates of B. catarrhalis from sputum and middle ear effusions were mixed with more traditional respiratory tract pathogens such as Haemophilus influenzae or Streptococcus pneumoniae or both (Shurin et al., 1983; Slevin et al., 1984). Although the β-lactamases of B. catarrhalis are predominantly cellbound (Farmer & Reading, 1986), the potential exists for sufficient enzyme to be released to contribute to treatment failures. They are, however, particularly susceptible to inhibition by clavulanic acid. Thus, with increasing evidence of tetracycline resistance among isolates of S. pneumoniae (Jacobs et al., 1978), β-lactamase inhibitors, combined with penicillins may be useful in such mixed infections.

The β-lactamases found in B. catarrhalis are different from those of other bacteria, such as H. influenzae and N. gonorrhoeae, which produce TEM-1 enzymes. At least two distinct types of β-lactamase have been identified in B. catarrhalis. The Ravaio enzyme (Farmer & Reading, 1982) has been found in the majority of strains (Stobberingh et al., 1984; Van Hare et al., 1987) and appears to be similar to the BRO-1 enzyme described in Sweden (Eliasson & Kamme, 1985). The enzyme from strain 1908 was distinguishable from that of the Ravaio strain by isoelectric focusing and differences in substrate and inhibition profiles (Farmer & Reading, 1982). The report by Stobberingh et al. (1984) also describes three additional β-lactamases not commonly found in other surveys (Nash et al., 1986).

The rapid increase in incidence of β-lactamase-producing strains led to speculation that β-lactamase production in B. catarrhalis was plasmid-mediated; however, most attempts to demonstrate this have been unsuccessful (Percival et al., 1977; Doern et al., 1980; Stobberingh et al., 1984; Pintado et al., 1985). Swedish workers have described conjugal transfer of a β-lactamase gene, specifying BRO-1, between Branhamella strains and also from Moraxella liquefaciens to B. catarrhalis (Kamme, Vang & Stahl, 1983; 1984); however, excessive nuclease activity did not allow conclusive characterization of extrachromosomal DNA. Other problems in the procedure were that the resistance determinant appeared very unstable and was lost unless potential donor cells were subcultured on to...
penicillin-containing medium immediately after primary isolation, and the fact that transconjugants so obtained could not act as secondary donors (Kamme et al., 1983). Subsequent refinements in the procedures have allowed the identification of extrachromosomal DNA; however, plasmids of similar size were detected in both ß-lactamase-positive and -negative strains (Kamme et al., 1986). Conclusive evidence of plasmid-mediated ß-lactamase production in B. catarhalis is still required. Attempts to transform a suitable recipient with DNA preparations have also been unsuccessful, presumably again because of excessive nuclease production. Hence it seems unlikely that, in general, the emergence of ß-lactamase-producing B. catarhalis is related to the spread of a plasmid, although the possibility of a transposable element cannot be discounted.

The question remains, therefore, why there has been such a rapid increase in ß-lactamase-producing B. catarhalis. Several theories have been advanced. The first relates to the widespread use of trimethoprim, both alone and in the form of co-trimoxazole, in the treatment of respiratory tract infections. B. catarhalis is intrinsically resistant to trimethoprim owing to the production of a dihydrofolate reductase (Then, 1979) and it has been suggested that trimethoprim therapy may select out strains of B. catarhalis that are both trimethoprim resistant and ß-lactamase producers (Calder et al., 1986). Lacey et al. (1980), however, could find no evidence of selection of resistant strains after trimethoprim therapy and a more likely selective pressure is the use of ß-lactam antimicrobials. Another possibility is that there has been an as yet undetermined change in virulence of strains of B. catarhalis which is in some way linked to ß-lactamase production.

An interesting point was raised by Calder et al. (1986) who reported that in 1983 53% of their patients apparently acquired B. catarhalis infections while in-patients, suggesting nosocomial spread within the hospital environment. In-vitro experiments demonstrated the survival of B. catarhalis for several weeks in sputum (McLeod et al., 1986) although the organism’s resilience has been known for some time (Wilson & Miles, 1964). Further investigations, including the development of a typing scheme, are required to determine the role of B. catarhalis in nosocomial infection.

Whether as a direct or indirect pathogen the presence of B. catarhalis in clinical specimens should be reported. The ability of any isolate to produce ß-lactamase should be determined so that appropriate antimicrobial chemotherapy can be instituted if required.

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References


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