condition change. Furthermore, an intravenous dose would be necessary as data based on a single intramuscular dose might be unreliable.

In summary it seems that a pharmacokinetic approach to dosage of aminoglycosides, whether by nomogram or calculation, can give the clinician more confidence in the resulting serum concentrations, and is certainly superior to giving fixed doses. For some patients this is all that is needed, but for the groups of patients mentioned above, initial dosage by nomogram must be followed by assays of serum concentrations.

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References


Ampicillin resistance in *Haemophils influenzae*

In 1972, an ampicillin resistant type B *Haemophils influenzae* was isolated from the CSF of a child with meningitis who subsequently died (Gunn, Woodall, Jones & Thomsberry, 1974). In 1974 Thomas, McReynolds, Mock & Bailey reported the occurrence of two more fatal cases of *H. influenzae* meningitis associated with the isolation of ampicillin-resistant organisms. All three of these patients were treated with ampicillin, the results of sensitivity testing not becoming available until after their death. Following this latter report further ampicillin-resistant strains were soon recorded by a number of centres both in the U.S.A. (Tomeh, Starr, McGowan, Terry & Nahmias, 1974; Khan, Ross, Rodriguez, Controni & Sz, 1974; Thornsberry & Kirven, 1974a) and Great Britain (Turk, 1974; Clomy & Harper, 1974; Williams & Cavannah, 1974; Mackintosh & Dadwell, 1974).

It was soon established that the resistance exhibited by these organisms was mediated by a penicillinase enzyme (Williams, Kattan &
Cavanagh, 1974; Khan, Ross, Rodriguez, Controni & Saz, 1974) and further characterization showed it to be constitutive, largely cell wall bound, and similar in substrate profile to the class IIIa (TEM type) β-lactamase of Enterobacteriaceae (Farrar, Jr. & O'Dell, 1974; Madeiros & O'Brien, 1975).

We have recently undertaken a survey to determine the current prevalence of ampicillin resistance in England and Scotland. Eighteen laboratories co-operated by sending all their isolates of H. influenzae to The London Hospital Medical College from February to April 1977 together with the results of their antimicrobial susceptibility testing. It was found that the overall incidence of ampicillin resistance among the 952 strains received was 1.5%. Resistance was defined as a strain having an MIC of 4 μg/ml or greater and all such strains were demonstrated to be β-lactamase producers. Only minor geographical variations were apparent. No resistant isolates were received from 8 centres and the highest resistance rate, in Bristol and Epping, was only 4%.

A further aspect that we explored was to compare the incidence of ampicillin resistance in encapsulated and non-encapsulated strains. Of 902 non-encapsulated strains 10 (1.0%) were ampicillin resistant. However of only 32 strains of Pittman type B received, 3 (9%) were resistant. Although these latter figures are small they do conform to the results of Khan, Ross, Rodriguez, Controni & Saz (1974), Nelson (1974) and Smith (1976), who recorded the resistance among type B strains in the U.S.A. to be 10%, 7% and 11% respectively, though it should be pointed out that Brotherton, Lees & Feigin recorded a resistance rate of only 1.5% among 269 type B strains isolated between July 1974 and January 1976 at the St. Louis Children’s Hospital, Missouri.

It is interesting to note that soon after the first reports of ampicillin resistance, surveys performed on randomly selected populations of H. influenzae revealed a surprising level of resistance. In 1974 Williams & Cavanagh could already report a resistance rate of 5% in Stafford, and in the U.S.A. Khan et al. (1974) and Nelson (1974) were able to record rates of 10% and 7% among strains of type B. In view of the fact that many surveys of antibiotic resistance in H. influenzae in strains isolated prior to 1974 had revealed universal sensitivity to ampicillin (e.g. Yow, 1969; McLinn, Nelson & Haltalin, 1970; Khan et al., 1974; Williams & Andrews, 1974) it would seem that following its emergence, the dissemination of resistance within the species must have occurred at a very rapid rate. The results of our present study would indicate, however, that following this initial event, little increase in resistance has occurred.

The correlation of in vitro resistance to in vivo response is clear from the number of reports of treatment failure associated with ampicillin therapy in infections produced by β-lactamase producing strains of H. influenzae. A reliable means of testing this organism’s susceptibility to the drug is thus essential. The vagaries of antimicrobial susceptibility testing of this fastidious organism have previously been discussed by McLinn, Nelson & Haltalin (1970), Clymo & Harper (1974) and Marks & Weinmaster (1975) who have emphasized the variations provided by different media and varying inoculum sizes. A standardized disc diffusion test using Mueller-Hinton medium plus supplement C (Difco) and utilizing a 10 μg disc has been recommended by Jorgensen & Lee (1977). Cavanagh, Kattan & Sykes (1976), however, recommended the use of a 2 μg disc and our recent experience would certainly support the use of this latter disc rather than the more conventional 10 μg one. One of the disturbing features of our survey was that only 5 out of 14 β-lactamase producing strains were correctly identified by their sending laboratory as being ampicillin resistant. A variety of different media had been used by the centres involved and the only common factor in the precision with which resistant strains were identified was the ampicillin content of the disc used. Only 2 out of 8 resistant strains were correctly reported by laboratories using discs of 10 μg content, whereas 3 out of 4 resistant strains were correctly reported by laboratories using either 5 μg or 2 μg discs. One laboratory used discs containing 25 μg of ampicillin and reported both of its β-lactamase producing strains as ampicillin sensitive.

Although β-lactamase production is not of course the only possible mechanism, its presence does provide good presumptive evidence of resistance. To this end a number of rapid methods have been devised for its detection (Thornsberry & Kirven, 1974; Catlin, 1975; Escamilla, 1976; Jorgensen, Lee & Alexander, 1977). Perhaps the easiest of the techniques devised employs the chromogenic cephalosporin substrate described by O’Callaghan, Morris & Kirby (1972). Its application to β-lactamase detection in H. influenzae has been outlined by Kattan (1975).
and Kammer, Preston, Turner & Hawley (1975). The former author describes how colonies can be tested for β-lactamase production by simply picking them off a plate and touching onto filter paper strips impregnated with the reagent. The test can be performed either on colonies present on a primary isolation plate prior to the performance of formal susceptibility testing or as a confirmatory procedure on organisms showing a reduced zone of inhibition on a disc diffusion sensitivity plate.

The low incidence of ampicillin-resistant non-encapsulated strains in the U.K. should not at present seriously limit the use of ampicillin in respiratory tract infections. However, as there are indications that the resistance rate may be higher in type B strains than in the non-encapsulated variety, it would seem advisable to consider initiating therapy in children with serious infections in which H. influenzae is strongly suspected to be the aetiological agent with chloramphenicol, and to change to the potentially less toxic ampicillin only when reliable sensitivity tests, which should if possible include a method for detecting β-lactamase production, show the organism to be sensitive.

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Control of herpes virus infections by drugs or vaccines?

Herpes viruses cause a wide spectrum of clinical illness including the relatively common oral lesion, herpetic keratitis, venereal infections and, more unpleasantly, herpes encephalitis. Two types of herpes virus (I and II) exist and although formerly it was considered that type II virus was restricted to the genital regions and that oral infections for example were caused by type I virus, there is now evidence that, in young persons at any rate, up to a third of genital isolates are type I (Chang, 1977).

A small upsurge in papers relevant to the control of herpes virus infections both by chemoprophylaxis and by vaccination has recently appeared and many describe encouraging results. The American antiviral substances programme has now published the results of its 5-year-long multicentre placebo controlled study of the purine nucleoside analogue vidarabine or Ara-A (Whiteley, Soong, Dolin, Galasso, Ch'ien & Alford, 1977), which had been shown previously to be effective for systemic therapy of herpes zoster infections in immuno-compromised persons (Whiteley, Ch'ien & Dolin, 1976). The trial studied 28 virologically proven cases of encephalities caused by herpes type I. Brain biopsy of the focal area of involvement was obligatory for admission to the series. Placebo or drug were administered intravenously at a dosage of 15 mg/kg/day for a 12-h period for 10 days. In summary, treatment reduced mortality from 70 to 28%, a significant decrease, indicating the compound to be considerably more active than idoxuridine or Ara-C which have been used in previous trials (Longson & Bailey, 1976). Of great interest was the observation that over half the survivors had only moderate or no neurological after effects. In fact the reduction in mortality was significant enough for the controlled trial to be stopped for ethical reasons. There are some reservations at this stage however. Clinically, once the comatose stage was reached, therapy was shown to be futile and 57% of comatose patients died in spite of therapy and all the survivors were severely debilitating. Ara-A is an insoluble compound and its administration in large volumes of fluid was a problem of some importance. Clearly there is a lot of work to be done yet investigating such parameters as optimal drug dosage, usefulness of more soluble molecular forms of Ara-A and, of great importance, the development of more rapid and reliable diagnostic methods for herpes virus infections. The year 1976 saw two large gatherings of virologists in New York and London and both discussed hopefully the possible future demise of the virus in the face of more potent antivirals. The New York meeting, recently published (Third Conference on Antiviral substances, 1977) spent the first morning discussing the potential of Ara-A. Data concerning the usefulness of the more soluble Ara-AMP, at least in the treatment of experimental keratitis (Falcon & Jones, 1977) as well as studies of Ara-A in tissue culture and in laboratory animals was discussed at the Society's 2nd meeting on antivirals in London. Also, other compounds are on the horizon including phosphonoacetic acid (Shipkowitz et al., 1973) which appears to have a specific inhibitory effect on the virus induced DNA polymerase. It has already excited the interest of molecular virologists but clinical application may be a long way off.

Both antiviral drugs and vaccines need to be considered in attempting to deal with the important uncontrolled virus diseases like herpes, influenza and hepatitis. Herpes-vaccine-virologists have tended to centre their interest around the potential oncogenic effects of herpes viruses. Herpes type 2 has been linked with cervical cancer (Rapp, 1973) while more certainly Epstein-Barr virus has been implicated in the aetiology of African Burkitt's lymphoma (Epstein, 1976) and nasopharyngeal carcinoma. Certainly Marek's disease lymphoma in chickens is prevented very