Antibiotic policies, practices and pressures

Two evolutionary events in medical practice during the antibiotic era are of much concern. They are: the high incidence of nosocomial infections of clinical importance, and the emergence of antibiotic resistant bacteria, which cause many of these infections and sometimes spread to the flora of the community. The former is at endemic proportions, estimated by some to utilize over 10% of hospital care (Freeman, 1977). The latter creates rapid obsolescence of valuable therapeutic drugs and causes excess morbidity and patient fatality rates. Both problems are in some respects iatrogenic and must affect our medical awareness, policies and practices. In most places it has become recognized as desirable, or required, to have a hospital infection control committee (officer) with responsibility and authority for surveillance and recommending antibiotic use policies. Although some standardization has been achieved in the definition of nosocomial infections, (Eichkoff, Brachman, Bennett & Brown, 1969; Editorial report, 1977) the kinds, frequency and interpretation of measurements are not uniform. The scientific basis for the antibiotic policy, the effect of its implementation and how to measure the effects are even more uncertain. Under these circumstances it is important for academic physicians and microbiologists with an interest in infectious diseases and antimicrobial chemotherapy to continue to address these problems with critical examinations of the rationale and validity of recommendations and practices.

Although there is a relation between hospital acquired infection and antibiotic use, the rate of nosocomial infection is primarily the result of other factors (Eichkoff et al., 1969; Editorial, 1977). On the other hand the emergence of antibiotic resistant strains is directly related to antibiotic use owing to the selective pressure favouring the overgrowth of resistant organisms (Finland, 1971). These strains may or may not have an advantage in colonization and lateral transfer causing nosocomial infections, but the elimination of the normal drug sensitive flora can provide opportunities for relatively noncompetitive multiplication. Sometimes these factors combine to augment the rate of occurrence of nosocomial infections with resistant strains into local epidemics (Price & Sleigh, 1970; Casewell, Dalton, Webster & Phillips, 1977). Overall, however, the rate of nosocomial infections is rather independent of antibiotic use, is quite constant for a particular patient facility and has limitations on the potential for procedural reduction under the present medical technology (Editorial report, 1977; McGowan, Parrott & Duty, 1977). Antibiotic practices tend to select the etiology and influence the outcome of nosocomial infections, and sometimes their rate of occurrence.

The effect of withdrawal of all or nearly all antimicrobial drugs from clinical use in the control of local epidemics provides the experience justifying such action (Price & Sleigh, 1970; Acot, Bouchchaud & Chabbert, 1977). However, it is always after the fact, it fails to benefit the patients who comprise the epidemic, denies the advantage of antibiotic prophylaxis to some, is untenable when the treatment of infection is indicated, and often requires temporary closure of the unit as complete surrender of the valuable uses of antibiotics to our inability to control drug resistant infections in any other way. Although acceptable or even necessary in special circumstances, the withdrawal or stringent restriction of antibiotic use is not a realistic or practical basis for developing a hospital antibiotic policy. Also the effectiveness of withdrawing one or several drugs in eliminating the resistance gene from remaining strains is by no means certain and differs for different drugs, different bacterial species, and different mechanisms of resistance (Petrocheilou, Grinsted & Richmond, 1976; Petrocheilou, Richmond & Grinsted, 1977; Anderson, 1974). In as much as plasmids with R-factors did not originate with antibiotic use, it is obvious that they can persist in the absence of any medicinal
administration of antibiotics. The amount and practices of drug use, however, can dramatically affect the frequency, transferability and the evolutionary composition of the antibiotic resistance specifying genes located on plasmids or in extrachromosomal DNA (Datta, 1974; Drews & Hogenauer, 1977). On the other hand, the competitive survival of selective genetic mutants is more often dependent on the antibiotic-related advantage, and if so, they disappear in its absence. In the past twenty-five years of intensive world wide development and use of antimicrobials, an abundance of plasmid-borne R-factors has been selected, multiplied, transferred and added to within their biologic compatibilities. This process, rather than specific resistant strains or species has clearly emerged as the major force confining antibiotic utility. One can be sure that the process will continue and with the higher level of distribution of these genes, antibiotic selective pressure may more often not be the only or perhaps even the principal factor in their acquisition or survival in the bacterial flora of a patient (Richmond, 1977).

To advance the rational basis for our policies and practices, clinical microbiologic investigations must determine and distinguish, if possible, when nosocomial infections with antibiotic resistant organisms are primarily a consequence of qualitative changes in the flora associated with antibiotic use independent of the prevalence of antibiotic resistance, and when the infection rate is enhanced by the emergence of specific resistant strains or species. The former impinges seriously on hospital practices, such as prophylaxis, duration of treatment, the kinds of patients treated, and the spectrum of antibiotics or antibiotic combinations used. The latter depends on the microbial attributes selected and modified by the antibiotic action, such as relative growth rates, the transferability of R-factors within the species and between species, the form and persistence of plasmids, etc. Before we can have confidence in the effect of a directed antibiotic policy we must learn more about what happens to specific kinds of antibiotic resistances under different antibiotic restrictions and their course once the gene has become prevalent among hospital strains.

To expect restricted use of antibiotics or to control their trial in the sick is not likely to be a successful approach. The statistical experience in America over the past ten years has stabilized at a remarkably constant level of about 30% of all patients in acute care hospitals being given antibiotics (Jackson, 1974). There is a need to identify the factors, other than use per se, that are associated with high rates of nosocomial infections and those related to the emergence of unwanted microbial characteristics, and the relations between the two. For example Acar has found that bacterial isolates from the community rarely carry more than one resistance factor whereas more than one-half of clinical isolates in hospitals have more than one, but strains with high multiple resistances are infrequent until after the eighth day in the hospital (Acar et al., 1978). Others have found that an effect of some kinds of antibiotic treatment increases the ability to transfer resistances (Finland, 1971).

Measurement and distinction of these effects in clinical material is not simple because of concurrent events. Also the biology is complex. Sometimes R-factors are associated with plasmids mediating virulence; plasmid genes can even be incorporated into the species chromosome and vice versa (Drews & Hogenauer, 1977). However, having recognized the possibilities of these associations, the direct relations among them are sufficiently random to permit definition of the primary effects in antibiotic resistant nosocomial infections. As the basic microbiology of plasmid-borne and mutational resistance to antibiotics is advanced there are opportunities and responsibilities available to the infection committees and microbiologists in centers with the interest and capability to observe the clinical and epidemiologic meaning of some of these events. The relative persistence and clustering of resistant genes whose prevalence has been increased by previous antibiotic use can only be determined in the clinical setting. Additional controlled observation of the effect of antibiotic practices on the level and persistence of specific resistant strains and the frequency of nosocomial infections should be long-term goals in the data collection of hospital infection committees.

If a hospital infection committee is to make distinctions between the effect of practices and drugs, certain prerequisites are necessary. A fundamental one is that they have available the means to identify the reason for use. This will permit the relation of practice procedures to the objective and to the effect it exerts on the microbial flora and acquisition of nosocomial infection. In a recent analysis of antibiotic use in a representative sample of hospitals in America (Interscience Com-
combination with other drugs will continue with lactamase resistant cephalosporins, usually in the increasing availability and use of β-lactams (Drews & Hogenauer, 1977). It is likely that the use of one antibiotic in the group may serve to maintain other resistance capabilities and presumably in vitro. Thus antibiotic resistant bacteria to the rate of nosocomial infections and the emergence of bacterial resistance. A surprising finding in the study noted above was that the mean duration of antibiotic prophylaxis was the same as for therapeutic use. This is incongruous and deserves further examination. In therapy a high proportion of the total antibiotic use was given to a small number of severely ill patients, often having a fatal outcome. Thus, there are opportunities to examine our practices independent of the overall use or non-use of antibiotics. With the accumulation and analysis of such experiences, better practices can be devised and recommended.

The question of relating the prevalence of antibiotic resistant bacteria to the rate of nosocomial infection also requires local information. In our recent survey β-lactam antibiotics accounted for 50 to 60% of the total in hospital antibiotic use; expectations are that the proportion will continue to increase. In our own hospital more than one-half of the bacterial isolates belonging to the Enterobacteriaceae have the capacity to produce β-lactamase providing them with a basis for resistance to ampicillin, some other penicillins and cephalosporins. The patterns of antibiotic resistance to various drugs often cluster in different groups that are characteristic of the particular hospital or locale (Drews & Högenauer, 1977; Acar et al. 1977). Usually these can be transferred together in vitro and presumably in vivo. Thus the use of one antibiotic in the group may serve to maintain other resistance capabilities (Drews & Högenauer, 1977). It is likely that the increasing availability and use of β-lactamase resistant cephalosporins, usually in combination with other drugs will continue to heighten the proportion of surviving bacteria carrying plasmids with various constellations of antibiotic resistances.

If we are to answer some of the questions about the relation of the prevalence of drug resistance to the frequency of nosocomial infections and the resultant morbidity, continuing systematic studies must be available to the infection control committee. This will require interest, perception, tenacity and fiscal support. Without it antibiotic policy runs the risk of being arbitrary, authoritarian, empiric, and often wrong.

Antibiotic use and antibiotic policies in hospitals continue to be haphazard in the sense that personal preferences, uncontrolled and sometimes misinterpreted experience govern practice. Other than withholding antibiotics or restricting their use in emergencies, no one has the wisdom, confirmed by data, to establish optimal programmes for general application. Our practices have permitted a continuing high rate of nosocomial infections and an increasing proportion of the bacterial flora that carry antibiotic resistance factors. Although great advances have been made in the molecular biology of antibiotic resistance the interpretation of the importance of the various factors must be determined in the clinics and hospital wards. It provides new opportunities to replace opinion and logic with data if goals are set and systematic observations are made. There is considerable room for improvement of practices that could decrease the antibiotic selection pressure without removing drug availability or the clinical benefit expected. In addition we need to develop studies in the clinical setting to learn the long term biologic importance of antibiotic resistance resulting from the therapeutic and prophylactic practices. The proportion of bacterial isolates carrying one or more antibiotic resistances is progressively rising. The cluster patterns, the effect on virulence (association with disease) and the rise, fall or persistence of different factors in relation to the use or removal of specific drugs are important questions for which we need clinical answers. The next thirty years of antibiotic development will not reproduce the past. Our skill and selective pressure on antibiotic use must be developed to match that of the antibiotics on bacteria.

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References


Induction of hepatic drug metabolizing enzymes and pregnancy while taking oral contraceptives Rifampicin acts as an inducer of hepatic drug metabolizing enzymes in man and in the mouse. Administration of 50 mg/kg rifampicin i.p. for 6 days leads to an induction of hepatic enzymes in the mouse, but not in the rat. Male ICR Swiss mice evidenced a 20% increase in liver weight, a 50% increase in cytochrome P450, a 43% increase in NADPH cytochrome c reductase, an 85% increase in ethylmorphine N-demethylation, a 77% increase in zoxazolamine hydroxylation, and an 89% increase in 17β-oestradiol metabolism (Pessayre & Mazel, 1976). In humans, chronic administration of rifampicin (e.g., 450 to 600 mg/day for 7 days) has been shown to lead to a reduction in the plasma half-life of rifampicin (Furezs, 1970; Curci, Bergamini, Delli Veneri, Ninni & Nitti, 1972) and warfarin (O'Reilly, 1974). Disturbances in cortisol metabolism have been reported, and in patients with Addison's disease, crises may be precipitated when rifampicin is administered chronically (Edwards, Courtenay-Evans, Galley, Hunter & Tait, 1974). Mean cortisol production rate was shown to be increased from 14±4±0-8 to 23·0±1·6 mg/24 h in 4 patients who had received 600 mg rifampicin daily for 6 weeks (Edwards et al., 1974). Chronic rifampicin had an adverse effect on renal allograft function, presumably due to increased metabolism of exogenously administered glucocorticoid (Baffington et al., 1976). Chronic rifampicin was shown to precipitate methadone withdrawal, which was correlated with a reduced plasma methadone half-life and increased urinary excretion of pyrroldine, a major methadone metabolite (Kreek, Garfield, Gutjahr & Giusti, 1976). Smooth endoplasmic reticulum was also increased in patients receiving chronic rifampicin (Jezequel, Orlandi & Tenconi, 1971).

Rifampicin has also been shown to dramatically increase aromatic hydroxylation rate, and this observation has served to explain pregnancy occurring during concurrent rifampicin and oral contraceptive administration (Hakim et al., 1971; Nocke-Finck, Breuer & Reimers, 1973; Bolt, Kappus & Bolt, 1974;