What resistance means to the Prescriber

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It is difficult to imagine life in a modern health service without antibiotics. They undoubtedly form the backbone of many of the important advances in modern medicine, allowing invasive diagnostic and therapeutic interventions that would not otherwise be possible due to infection.

To contemplate a "post antibiotic era" has potentially huge implications, far beyond the ability, or not as the case may be, to be able to treat a specific infection. It is, however, this rather narrow, specific implication of resistance that I will consider here, namely how resistance compromises the treatment of infection in the 2010s.

Resistance of course, means different things to different people. To the microbiologist it usually means the presence of a resistant mechanism that increases the wild type MIC (and/or MBC although this will not be considered here). To the clinician, what is more important is the clinical breakpoint and whether the MIC is above this and if so, how much above it i.e might the infection respond to altered dosing schedules such as higher dose or prolonged infusion. Technically, such an organism might be better classified as intermediate.

Crudely put, resistance to the prescriber usually means the potential for increased chance of failed treatment response, increased length of stay and morbidity and even death i.e an increased burden of disease. On a global scale this is, arguably, very evident in the increasing problems seen in most hospitals from hospital acquired infections, this despite huge resource being put into infection control. At an individual level, the main immediate issue is choosing correct empiric therapy which is more difficult with increasing resistance to first line agents. Inappropriate empiric therapy is clearly associated with poor outcome, however measured. Furthermore, second line agents such as vancomycin may be associated with inherently poor outcomes compared with β lactam treatment in the case of Staphylococcal infection.

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Historically prescribers are slow to acknowledge the problem of resistance, usually considering this someone else's problem. Consequently, empiric policies can be slow to change, often lagging several years behind changes in resistance. Moreover, prescribers do not associate their prescribing with resistance in their patients. Unfortunately the evidence is now overwhelming that both these views are false. In the UK at least, I have noticed attitudes changing in just the past few years, particularly with the advent of MRSA and multi resistant, hyper toxin producing epidemic strains of *Clostridium difficile*. If we look at empiric therapeutic choice over the past 6 decades of the antibiotic era, it is quite easy to see how prescribing has changed, primarily due to resistance but also, of course, due to the timely advent of new antibotics, developed specifically to solve these resistant problems. For example, empiric treatment of *E.coli* septicaemia has ranged from tetracycline to chloramphenicol to aminoglycoside, then to ampicillin, co-trimoxazole, mezlocillin, temocillin, co-amoxiclav, cephalosporin in various guises, quinolone, piperacillin-tazobactam and now increasingly to carbapenem. Now, in some areas, due to the lack of new agents, old agents are again being used, to protect carbapenems from overuse. In the UK these agents include cotrimoxazole, gentamicin and temocillin.

The effects of antibiotic prescribing on resistance are often easier seen at a population level than at an individual level and in hospital rather than the community, but several recent papers have identified the risks to individuals of comunity antibiotic prescribing especially for urinary tract infection.[1,2,3] Generally though, there is still little perception of the damage done to commencal flora by antibiotics, with most concern being for development of resistance in pathogens. From a patient perspective, probably it has been the relatively recent advent of MRSA that has alerted the general population to the problems, but their focus is more on the infection control aspects of MRSA rather than antibiotic stewardship. Recent threats of pan resistance have caused noticeable activity in the medical press, particularly with the description of New Delhi β lactamase. Doctors from different backgrounds will inevitably have different perspectives. Perhaps surgeons have traditionally been the most restricted in their vision of the problems and this still seems to be the case.[4]

In addition to choices of antibiotics and pharmacodynamic/pharmacokinetic (PK/PD) considerations to optimise dosing schedules, both of which have already been mentioned, the other areas that are seeing major changes in practice, because of resistance are the tendencies to shorter courses of antibiotics, the use of antibiotic combinations[5] and also less use of antibiotics

where the benefits of a prescription are doubtful. This has seen major revision of antibiotic use in surgical practice and for community respiratory infections, the majority of which are viral. A further consideration in the context of diseases where a prescription is definately indicated is the severity of the illness and at what resistance level to change empiric therapy. For Staphylococcal bacteraemia a MRSA rate of 10% may well drive a change to empiric use of a glycopeptide but for cystitis, even a trimethoprim resistance rate of 30% may not disuade its use as first line therapy as many cases are self limiting and there will not be a 30% failure rate.

Recent estimates in the European Union for the costs of selected multidrug resistant bacteria are 25,000 deaths per year and 1.5 million EUR[6]. In the USA these are $20-30,000 per patient excess hospital costs, excess societal costs of $10-18 million and double the morbidity (attributable mortality 6.5%)[7]. In a recent survey of European Intensive Care Unit physicians; 82% considered multidrug resistance to be a major or significant problem. More than half respondents had treated at least one (in some cases more than 10) case of extensive drug resistance or pan drug resistance in the past 6 months.[8] In developing countries 70% of hospital acquired neonatal unit infection couldn't be treated using World Health Organisation recommended drugs.[9]

In the UK and USA MRSA costs have been estimated at >5 and 20 billion dollars respectively. These figures include the societal costs of lost productivity.[10]

In conclusion, resistance is an increasingly worrying problem with huge medical and societal costs. Although it has only recently made a high profile impact on medical practice, infact policies to cope with it have been developed, albeit slowly, since the beginning of the antibiotic era.

References

1. Vernaz N, Huttner B, Muscionico D, Salomon J-L, Bonnabry P, López-Lozano JM, Beyaert A, Schrenzel J & Harbarth S. 2011. Modelling the impact of antibiotic use on antibiotic-resistant *Escherichia coli* using population based data from a large hospital and its surrounding community. *JAC* **First Published online: January 19, 2011.**
2. van der Starre WE, van Nieuwkoop C, Paltansing S, van't Wout JW, Groeneveld GH, Becker MJ, Koster T, Wattel-Louis GH, Delfos NM, Ablij HC, Leyten EMS, Blom JW, van Dissel JT. Risk factors for fluoroquinolone-resistant *Escherichia coli* in adults with community-onset febrile urinary tract infection. *J Antimicrob Chemother* 2011;**66**:650-656.
3. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. 2010. Effect of antibiotic prescribing in primary cae on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010;**340**:1120-1124
4. Lucet J-C, Nicolas-Chanoine M-H, Roy C, Riveros-Palacios O, Diamantis S, Le Grand J, Papy E, *et al*. Antibiotic use: knowledge and perceptions in two university hospitals. *JAC* **First published online: January 26th, 2011.**
5. Kumar A, Zarychanski R, Light B, Parrillo J, Maki D, Simon D, Laporta D, *et al.* Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: A propensity-matched analysis. *Crit Care Med* 2010;**38**:1173-1785.
6. European Centre for Disease Control and Prevention, European Medicines Agency. (2009) The bacterial challenge – time to ReAct. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/11/WC500008770.pdf http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/11/WC500008770.pdf
7. Roberts RR, Hota B, Ahmad I, Scott RD, Foster SD, Abbasi F, Schabowski S *et al.* Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. *Clin infect Dis* 2009;**49**:1175-1184.
8. Lepape A, Monnet DL, on behalf of participating members of the European Society of Intensive Care Medicine (ESICM). Experience of European Intensive Care Physicians with infections due to antibiotic-resistant bacteria, 2009. Euro Surveill 2009;14(45):pii=19393. http://www.eurosuveillance.org/ViewArticle.aspx?ArticleId=19393.
9. Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries *Lancet* 2005;365:1175-1188.
10. Gould I M. Costs of hospital-acquired methicillin-resistant Staphylococcus aureus (MRSA) and its contol. *Int J Antimicrob Agents* 2006;28:379-384.