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Narrow Versus Broad Spectrum Antibacterials

Factors in the Selection of Pneumococcal Resistance to β-Lactams

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Abstract

Streptococus pneumoniae represents an interesting model to discuss the relative impact of broad versus narrow spectrum antibacterials as potential selectors for resistance. Indeed, this pathogen is responsible for potentially severe infections in the community, and has a great capacity for acquisition of resistance to antibacterial agents. It has been the focus of many studies to elucidate some unique aspects of molecular biology, including the adaptive mechanisms responsible for emergence and spread of multiresistance.

In the past, the use of narrow spectrum agents was recommended in order to try to reduce the risk of selection of resistance. This concept is nowadays somewhat obsolete for several reasons. *S. pneumoniae* is able to acquire resistance to antibacterials belonging to different families of drugs through different molecular mechanisms. Thus, selection of multiresistant pneumococci can result from exposure to very different agents, including narrow spectrum as well as broad spectrum agents. *In vitro* studies have shown a different potential for selection of resistance among the β-lactam agents. Furthermore, several studies have more or less directly established a close relationship between the level of antibacterial use and the rate of selection of resistance. In addition to the overall amount of antibacterials prescribed in the community, several other factors have been shown to influence the rate of selection of resistance, including the use of doses that are too low, the length of therapy and the duration of bacterial exposure to long-acting agents compared to drugs with short half-lives.

Therefore, there are three main ways to control selection and spread of resistant strains: by (i) reducing the amount of antibacterials used; (ii) using optimal dosages (avoiding underdosing) and treatments of short duration; and (iii) reducing the risk of transmission among young children attending daycare centres or kindergartens. In order to help physicians reduce the number of unnecessary prescriptions, it is important to develop rapid tests to recognise the bacterial origin of a febrile illness and even more important to detect resistance to antibacterials. However, apart from rapid diagnostic tests for streptococcal pharyngitis, those tests are not currently available.

As a consequence, currently, the debate around narrow versus broad spectrum antibacterials remains a false debate. Physicians should use broad spectrum agents in many instances of upper or lower respiratory tract infection, taking into

consideration the probable pathogens and the risk of (multi)resistance to antibacterials. Once rapid diagnostic are available in community practice, allowing a precise diagnosis of the offending agent and its susceptibility profile, physicians will be able to add to their current criteria the selective potential for resistance of the antibacterials that appear to be active *in vitro*.

Streptococcus pneumoniae has been recognised as a human pathogen for 120 years.[1] It remains the most common worldwide cause of potentially severe illnesses such as community-acquired pneumonia and acute otitis media. In countries where vaccination has been responsible for declining rates of *Haemophilus influenzae* type b infections, it is now the leading cause of acute bacterial meningitis. Appropriate therapy notwithstanding, pneumococcal bacteraemia is still associated with high mortality. Young children, the elderly, and individuals with cardiopulmonary disease or immune compromise are more commonly affected and have the highest mortality. The global impact of disease caused by pneumococcal strains in terms of morbidity, mortality and overall burden to society are incalculable. Consequently, and as a result of contributions by many researchers, the pneumococcus has been the focus of abundant studies which have helped elucidate unique aspects of molecular biology. These include our nascent understanding of the multiple adaptive mechanisms that are responsible for the emergence and spread of penicillin-resistant and multidrug-resistant strains over the past decades.[2]

Penicillin dramatically improved the outcome of patients with pneumococcal infections, but development of resistance has been an inevitable consequence of antibacterial use. In the last decade, there has been a dramatic worldwide increase in the prevalence of penicillin resistance in strains of *S. pneumoniae* (PRSP). The basis of penicillin resistance is the genetic alteration of the targets for penicillin action, the cell wall synthesising penicillin-binding proteins (PBPs). As a result of the acquisition of PBP-encoding DNA from other streptococcal species, and clonal or horizontal spread of structural mosaic genes that encode for PBPs with reduced affinity for penicillins and other β-lactams, reduced susceptibility and high level resistance strains exist. Epidemiological, serotyping and genetic fingerprinting data are consistent with multiple clonality. PRSP with penicillin minimum inhibitory concentrations (MICs) >1 μg/ml have developed multiresistance.

Acquisition of a complete package (cassette) of DNA confers broad resistance to a number of antibacterials resulting in multidrug-resistant *S. pneumoniae* (DRSP). The catalogue includes unrelated drugs such as chloramphenicol, co-trimoxazole, macrolides, tetracyclines and aminoglycosides. Approximately 10% of PRSP are resistant to third generation cephalosporins, probably less to carbapenems.[3] Quinolone resistance is increasing,[4,5] resistance to quinupristin/dalfopristin is rare, and resistance to glycopeptides, already present in other streptococcal species, has not yet been reported but is possible. Factors not considered here, such as the volume of antimicrobial consumption in human communities,[6] immune suppression, poor infection control practices, increased use of invasive devices in medical wards, and widespread utilisation of antimicrobials in animal husbandry and agriculture have played a largely unmeasured role in the worsening situation of global resistance.

The magnitude of the problem has reached serious proportions and continues to grow. In the year 2002, we examine the possible consequences of treating patients infected with strains of *S. pneumoniae* resistant to all available antibacterials, and returning to pre-penicillin era morbidity and mortality at a much higher cost. Resistance is undoubtedly a public health threat; hence, societal and professional commitments to intervention are necessary. One intervention concerns the choice of antibacterial for therapy of pneumococcal infections.

1. Relationship Between Antimicrobial Use and Resistance

Two facts are generally acknowledged: (i) one essential factor in the emergence and spread of resistance genes, and therefore of resistant microorganisms, is the selective pressure of antibacterials, and (ii) overuse of antibacterials is an ongoing worldwide problem.

In vitro, sequential subcultures of susceptible *S. pneumoniae* in subinhibitory concentrations of antibacterials leads to increased MICs for that drug, and in the case of aminopenicillins, also for cephalosporins.[7,8] The recent dramatic expansion of PRSP and DRSP strains may be due in large part to similar phenomena occurring *in vivo*. By resulting in sub-lethal tissue concentrations, low daily doses and long treatment durations may more closely resemble the *in vitro* experiments and more effectively select resistant bacteria *in vivo*.[9,10]

At the individual and population levels, carriage of PRSP correlates with antibacterial consumption,[11] this is true also for DRSP. Previous antibacterial use by an individual is an independent risk factor for carriage or infection by PRSP.[10,12-24] The relationship has been established for hospital[25] and community-acquired infections,[9,11] as well as for β-lactam and non β-lactam agents.[11,21,26] At community or country levels, data on antimicrobial use and resistance are scant, and have often been collected without rigorous standards. Understanding and comparing such data is difficult. Although worldwide information linking antibacterial utilisation with resistance has limitations, in general, resistance is higher in areas of high consumption and lower in areas of low consumption.[27,28] An increasing prevalence of resistance has been described associated in time to increasing aminopenicillin sales or use.[11,29,30] Increasing β-lactam resistance correlates with increased use of macrolides with very long half lives.[31] Interestingly, increased use of cotrimoxazole is a significant risk factor for PRSP carriage in Sweden.[21] The problem is compounded by the fact that variations in the utilisation of antibacterials between or even within countries or cities are the rule.[28,30]

The resistant phenotype can be lost,[32] but very few published studies have addressed the substantial possibility of meaningful -although almost certainly not complete- reversibility of resistance by decreased utilisation of antibacterials,[33,34] as may be the case. Intervention trials trying to answer this question are ongoing in different countries.

2. Consequences of Acquisition of Resistance

The procurement of altered PBP genes provides pneumococci with the means to survive in environments containing penicillin and other antibacterials. This advantage has been hypothesised as carrying a price for the bacteria. Resistant organisms would have diminished competence to strive if the selective pressures were removed. Changes in the peptidoglycan peptide composition and chemical structure of resistant pneumococcus have been documented *in vitro*.[35] *In vivo*, penicillin resistant (and not quinolone resistant-penicillin susceptible) strains of pneumococcus belonging to diverse serotypes exhibit markedly diminished murine virulence,[36,37] and a similar association has been reported for other bacterial species.[38] In humans, pneumococcal pneumonia has been linked to milder,[39] comparable [40] or more severe[41] clinical manifestations when the causative agent was PRSP. Unequivocal demonstration of a clinically apparent damaging alteration in resistant strains of *S. pneumoniae* is not presently available, but the altered properties of PRSP may have direct bearings on the clinical manifestations of pneumococcal disease.[2]

3. *In Vitro* and *In Vivo* Selective Effects of Antibacterials in Streptococcus Pneumoniae

Several factors should be considered regarding the *in vitro* and *in vivo* selective effects of antibacterials in *S. pneumoniae*.[10] These are, the number of bacteria, the mixture of penicillin susceptible and resistant organisms, the type of antibacterial

used, the pharmacokinetic and pharmacodynamic properties of the drugs, their dose administration regimens and the compliance of the patient. *In vitro*, it appears that oral cephalosporins select more for resistance than amoxicillin, depending on their initial MIC value.[42] *In vivo*, changes occur in the nasopharyngeal flora of children receiving either cefpodoxime or amoxicillin/clavulanic acid prescribed for the treatment of acute otitis media.[43] Carriage of PSSP decreased from 32% before treatment to 6% after treatment. Among children carrying pneumococcus at the end of their treatment, the percentage of PRSP increased from 42% before therapy to 75% after treatment. In over half of the children, the same serotype was encountered at the end of therapy. Furthermore, the percentage of PRSP was greater at the end of cefpodoxime than at the end of amoxicillin/clavulanic acid therapy. Thus, many factors other than the extent of the antibacterial spectrum are important for the resistance selective potential of the drug.

Table I. Markers associated with carriage or infection by resistant strains of *Streptococcus pneumoniae*[a]

Recent use of an antibacterial including:
therapeutic use
prophylactic use
β-lactam
co-trimoxazole (trimethoprim/sulfamethoxazole)
long acting macrolides
repeated courses
Living in an area of high prevalence of resistance
Young and old age
In children, attendance at daycare centres
White ethnicity
Prior hospitalisation
Nosocomial acquisition
Site of isolation:
upper respiratory tract
Otitis media related conditions:
patient prone to otitis media
otitis unresponsive to amoxicillin therapy
HIV infection

a Broader therapeutic options must be kept open or can be applied when such a history is retrieved.

4. Practical Aspects in the Selection of Narrow Versus Broad Spectrum Antibacterials for Pneumococcal Infections

Choosing a drug with the appropriate spectrum of activity will always remain important. However, choosing the correct drug, dose, dose interval and duration of therapy may more efficiently provide clinical benefit while contributing less to resistance[9] than choosing the drug with the narrowest spectrum.

Historically, the concept of separation between narrow versus broad spectrum antibacterials has had importance. Currently though, the high level of resistance achieved, the fact that narrow spectrum antibacterials do select for broader spectrum resistance, and the persistent lack of rapid and reliable methods that permit the positive diagnosis of pneumococcal infections, make the separation issue less relevant. In the near future, the impact of antibacterials on bacterial ecology will rest on the magnitude and appropriateness of utilisation more than on the selection of narrow versus broad spectrum compounds. Therefore, emphasis must be placed on judicious use. Epidemiological and historical knowledge, such as the presence or absence of markers of infection by resistant pneumococci (table I), as well as clinical information such as site and severity of the disease, and the presence or absence of associated host conditions, must guide general therapeutic and specific antibacterial choices.

At the bedside, pragmatism must be favoured over excessive risk even if that means utilising a broad over a narrow spectrum drug. For example, a fluoroquinolone might be chosen over amoxicillin for particular patients with pneumonia, high-dose of an appropriate cephalosporin plus vancomycin for many patients with meningitis, tympanocentesis for patients with otitis media who are unresponsive to treatment. Once chosen, the antibacterial must be used at the dose, dose interval and duration that best preserves both the health of the individual and the usefulness of the antimicrobial armamentarium.

5. Diminishing Selective Pressure

It becomes of primary importance to reduce selective pressure by any means currently available. The main point is to restrict antibacterial use to situations in which these agents are necessary. To reach this goal, it is necessary to improve initial and continuous education processes sensitising healthcare providers to this major health problem. The development of rapid diagnostic tests to help quickly diagnose bacterial disease – and even more rapidly recognise the susceptibility/resistance pattern of the causative bacteria – is able to improve the behaviour of prescribers. Once the need for an antibacterial has been established, the choice of the correct drug, according to what is known about the current susceptibility profile of potential bacteria, is the second most important step. Appropriate dose, dose interval and the shortest duration of treatment that cures the disease are other points to be considered.

To control the selection and transmission of PRSP, it is also important to avoid close contacts between young children in daycare centres as much as possible and to develop vaccines. The use of immunogens preventing infection by pneumococcal strains of the serotypes associated with resistance can have a dramatic effect not only on rates of nasopharyngeal carriage, but also in morbidity, mortality and cost associated with antibacterial resistance.[44-46]

6. Narrow Versus Broad Spectrum?

We may be past the time for consideration of narrow versus broad spectrum. However, it is tempting to postulate that if susceptibility patterns are at least partially reversed by the correct use of ecologically preferable antibacterials, and rapid aetiological diagnosis of pneumococcal infections becomes available, the issue of narrow versus broad spectrum will regain its previous importance in the preservation of antibacterial susceptibility in *S. pneumoniae*.

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