# Future Use of Newly Developed Antimicrobial Agents against Resistant Gram-positive Cocci

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What I would like to talk about today is the activity of various existing and also experimental agents against pneumococcus strains with raised penicillin MIC's. Many of these antimicrobials we are very well acquainted with and many of them are still experimental. But because of the increased incidence of resistant pneumococcal strains worldwide it is important to know what is available, what is in the pipeline and on the horizon, and approximately how long these experimental drugs will take if they do make it to market.

Now first of all I would like to emphasize, and Dr. Jacobs will emphasize this as well, what we mean by penicillin resistance. In the late 1970's on the basis of regression lines, Dr. Jacobs's group in South Africa divided pneumococci into three groups: (i) those susceptible to penicillin with MIC's ¡ Â0.06 § ¶/ml (ii) those intermediate with MIC's between 0.125 and 1.0 § ¶/ml and (iii) those resistant with MIC's ¡ Ã2.0 § ¶/ml. It is really important to realized that, at the time these were done, there were no pneumococci with MIC's of 0.06 § ¶/ml. We are going to emphasize again and again that these breakpoints are completely empiric, and depend on many factors for interpretation. Dr. Jacobs has coined a better term for these strains as "penicillin challenged". There are several reasons for this problem in classification. The mechanism of penicillin-resistance in pneumococci is changes in penicillin-binding proteins. Therefore you do not have a clear bimodal distribution such as you do when antibiotics are enzymatically broke down such as chloramphenicol. Instead, a continum is obtained with penicillin. Also, whether a pneumococcus is resistant to penicillin clinically depends on the source from which is isolated. As will become very clear during the course of other presentations, the two sites which are the most problematic therapeutically are the ear(otitis media)and the cerebrospinal fluid(meningitis). For example, a pneumococcus with an MIC of 0.06 § ¶/ml in the blood and in the sputum may be regarded as clinically susceptible, whereas in the ear and most especially in the cerebrospinal fluid it should be reagrded clinically as having a higher MIC to penicillin. Again, a pneumococcus with an MIC of 0.125 or 0.25 § ¶/ml which is causing pneumonitis can be regarded as penicillin susceptible clinically because you can raise the dose of the ß-lactam therapeutically; however, such as a strain in the ear or in the cerebrospinal flluid is not clinically susceptible to penicillin. So our classification of penicillin susceptibility in the pneumococcus is not satisfactory.

Now, having said that I would like to go through a series of slides showing you the activity of various drugs some available, others experimental, against penicillin susceptible, intermediate and resistant pneumococci and these slides summarize surveys of people who I know and trust. They summarize findings from basically three groups; our group, a group in Barcelona and the group in Paris. If we first look at the penicillins, and you can see on this slide that the MIC's of penicillin G and ampicillin against penicillin susceptible, intermediate and resistant strains are identical. However, those of amoxicillin against mainly itermediate strains and sometimes resistant strains are usually one dilution lower than those of penicillin and ampicillin. Of course because the mechanism of penicillin resistance is not ß-lactamase mediated, addition of sulbactam to ampicillin and clavulanate to amoxicillin is without effect. When we look at other parenteral penicillin's we see that ticarcillin is not active against intermediate and resistant strains whereas mezlocillin and piperacillin are. Pipercillin will give a maximal MIC of 16 § ¶ml against a fully resistant strain compared to 128 § ¶ml or more for ticarcillin and this again may have therapeutic implications. Again, addition of clavulanate to ticarcillin and tazobactam to piperacillin is without effect.

Remembering the low MIC's of amoxicillin, let us now look at the activity of oral cephalosporins against these strains, specifically cefdinir, cefpodoxime, cefuroxime, cefaclor, cefixime, cefetamet, cefprozil and loracarbef. You can see that the MIC's even of the most active of these drugs, namely cefdinir, cefpodoxime, and cefuroxime, are several dilutions higher than those of amoxicillin. $MIC_{90}$ 's of the latter three drugs are between 1-4 § ¶ml against intermediate strains and 4.0 and 8.0 § ¶ml against fully resistant strains, compared to 0.125 to 1.0 § ¶ml against intermediate strains and 2.0 § ¶ml against fully resistant strains for amoxicillin. MIC's of cefaclor, cefixime, cefetamet and loracarbef reflect no activity at all against penicillin intermediate and resistant strains and cefprozil is marginally active at best against intermediate strains only.

Also extremely important as far as oral ß-lactams are concerned is the ratio between MIC's and achievable blood levels. When you combine these two it turns out that the only oral cephalosporin with activity which is fairly acceptable is cefuroxime. Cefpodoxime, for instance, looks good until you realize that it's peak blood level is approximately 2.5 § ¶ml and that shows you that, with an $MIC_{90}$ of 1-4 § ¶ml against intermediate strains, you can't use it. Cefprozil with an $MIC_{90}$ of 8.0 § ¶ml against intermediate strains yields MIC's which are right at the border of peak serum levels. When you compare all oral ß-lactams that are currently available, amoxicillin turns out the best. One oral cephalosporin currently available in Japan which really does look good against penicillin susceptible, intermediate and resistant pneumococci is cefditoren: the highest MIC's that we found with cefditoren were 2.0 § ¶ml against fully penicillin resistant strains. Cefditoren has the lowest cephalosporin MIC's against penicillin susceptible and resistant pneumococci of which we are aware.

There are two other oral ß-lactams which we need to discuss:(i) WY49605 which is the same as SUN/SY5555. This compound yields very low MIC's even to penicillin-resistant strains, with an $MIC_{90}$ against intermediate strains of 0.5 § ¶ml and an $MIC_{90}$ against resistant strains of 1.0 § ¶ml. The other compound, GV118819X or santetrinem, yields

MIC’s the same as those of WY49605. These two compounds both hold promise. As far as I know the WY compound is not being developed in Europe or in the U.S., but I think that sanfetrinem is. It is very important to realize that a compound such as WY49605 is in reality an oral carbapenem which, if abused, could create a powerful pressure to select highly resistant pneumococcus strains which would be very difficult to treat. The key with such powerful compounds is restriction and rational use.

In the next slide we are going to talk about the parenteral cephalosporins which really form the mainstay of treatment of systemic infections caused by these organisms. In the U.S. the two which are used are ceftriaxone and cefotaxime. These two drugs are used basically interchangeably: ceftriaxone has the advantage of 1-2 daily dosing. $MIC_{90}$’s even though they rise, are between 0.25 and 1.0 § ¶/ml for intermediate strains and 1.0 to 4.0 § ¶/ml for resistant strains. Cefpirome yields slightly lower MIC’s than cefotaxime and ceftriaxone. Cefpirome is available in Europe and is not going to be developed in the U.S. as far as I know. Cefepime yields MIC’s the same as ceftriaxone and cefotaxime. It has just been marketed in the U.S. with very little clnical information to go on as far as treatment of pneumococcal infections is concerned.

As far as the carbapenems are concerned, the two which are important in the U.S. and which are available are imipenem and, lately, meropenem. Both yield low MIC’s even though they go up as the penicillin MIC rises. Meropenem has an advantage, in that it does not seem to cause convulsions which imipenem has been described to do. These other two compounds, biapenem and BO 2727, as far as I know are being developed in Japan and not anywhere else that I am aware of.

The next group of drugs to be discussed are the quinolones. Because the mechanism of activity of quinolones is DNA gyrase inhibition, quinolone MIC’s are identical against penicillin susceptible, intermediate and resistant strains. Ciprofloxacin and ofloxacin $MIC_{90}$’s are between 1.0 and 4.0 § ¶/ml and fleroxacin and lomefloxacin ¡ Ã8 § ¶/ml. I don’t really believe that you should have pneumococcal breakpoints for ofloxacin for but NCCLS has approved these. Because MIC’s of ciprofloxacin and ofloxacin cluster around the breakpoint, these compounds should not be used to treat serious systemic pneumoccal infections. There are many other quinolones which are being developed. Ones which have been discarded because of toxicity are temafloxacin. CI 990, Win 57273 and Bay y3118. Levofloxacin, the *l*-isomer of ofloxacin has recently been approved in the U.S., with MIC’s 1-2x lower than those of ofloxacin, Sparfloxacin is available in Japan and the Philippines and also parts of Europe. Grepafloxacin, Bay 12-8039, clinafloxacin, DU-6859a and gatifloxacin are being developed. The $MIC_{90}$’s of sparfloxacin, grepafloxacin, Bay 12-8039 and gatifloxacin are basically the same approximately 0.25 § ¶/ml. Clinafloxacin has got low $MIC_{90}$’s of 0.125 § ¶/ml, and DU-6859A has the lowest $MIC_{90}$’s of all, 0.06 to 0.12 § ¶/ml. DU-6859A is also rapidly bactericidal in vitro. The napththyridones are related to the quinolones. Trovafloxacin is the important member of this group with $MIC_{90}$’s between 0.125 and 0.25 § ¶/ml. This drug has got a very wide spectrum of activity and should be a available worldwide within a year or maybe a little less.

The glycylcyclines have low MIC’s against pneumococci, and are much more active than tetracycline and minocycline. However, it seems to me that they are too toxic and that they are not going to be developed.

The oxazolidinones are experimental compounds with good activity against Gram-positive strains including pneumococci. The two which I have examined are U-100592 and U-100766, both of which yield MIC$_{90}$'s between 0.5 and 1.0 § ¶/ml. I am not sure whether these are going to be develped, but we hope so.

Now let us discuss the MLS(macrolide-lincosamide-streptogramin) group, first of all the macrolides. It is important to remember that when a pneumococcus is susceptible to one member of the macrolide group, it is susceptible to all of them. In other words if an organism is susceptible to erythromycin it will be susceptible to azithromycin, clarithromycin, josamycin and roxithromycin. For erythromycin susceptible strains clarithromycin yields MIC's a couple of dilutions lower than those of erythromycin. If, however, an organism is resistant to erythromycin it is resistant to all of the above named compounds. Clindamycin, a lincosamide, is slightly different: if an organism is susceptible to erythromycin it will be susceptible to clindamycin. However, if it is resistant to erythromycin there are strains resistant to erythromycin and all other macrolides, but susceptible to clindamycin. They are not very common but, they do exist. As Dr. Jacobs will inform you, the current methods that NCCLS have recommended for microdilution testing of pneumococci will often not detect clindamycin resistance properly. The one group of the macrolides which is really exciting are the ketolides. The MIC$_{90}$ of RU64004 against erythromycin suseceptible strains is 0.016 § ¶/ml compared to 0.06 § ¶/ml for erythromycin. Most dramatically, the MIC$_{90}$ of RU 64004 against fully erythromycin resistant strains with MIC's ¡ Ã128 § ¶/ml is 0.25 § ¶/ml. I am currently examing a second ketolide. We all hope very much that these compounds are going to be developed. They are active against *Haemophilus*, *Moraxella catarrhalis* and also against a wide range of other streptococci.

There are two streptogramins, the parenteral streptogramin RP 59500 and the oral streptogramin RPR 106972. Both of these are very active against pneumococcus strains irrespective of whether they are susceptible or resistant to penicillin or erythromycin with MIC$_{90}$'s of 0.5 - 1.0 § ¶/ml for RP 59500 against erythromycin susceptible and 1.0 - 2.0 § ¶/ml against erythromycin resistant strains. The oral compund yield MIC$_{90}$'s between 0.25 and 0.5 § ¶/ml irrespective of the macrolide or penicillin susceptibility of the strains. Both streptogramins are very rapidly bactericidal against pneumococci.

The glycopeptides currently include vancomycin and teicoplanin. Vancomycin is available all over the world and teicoplanin is available in Europe. A new experimental glycopeptide called LY333328 is the most active, with MIC$_{90}$'s of 0.016 § ¶/ml; teicoplanin yields MIC$_{90}$'s of 0.06 § ¶/ml - 0.25 § ¶/ml and vancomycin MIC$_{90}$'s 0.125 § ¶/ml - 0.5 § ¶/ml. Vancomysin plays an important part in the treatment of meningitis caused by penicillin intermediate and resistnat pneumococci, as you will hear. An organism will either be susceptible to cotrimoxazole, with MIC's of around 0.25 § ¶/ml - 0.5 § ¶/ml or resistant with MIC's > 4 § ¶/ml. Rifampin, although it is not an important part of the therapy of pneumococcal infections, is most often active against these strains, except in children tuberculosis hospitals who have been exposed to rifampin as a selective pressure because of treatment of conditions such as tuberculous meningitis.

So that Ladies and Gentlemen is what I have to say. I would like to leave you with the impression that the two infections where we do not have proper therapeutic modalities for infections cause by these penicillin challenged strains are otitis media and meningitis.