# GENERAL CONSIDERATIONS BY A CLINICAL BACTERIOLOGIST REGARDING ANTIBIOTIC THERAPY IN ACNE

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The relationship between potentially pathogenic and non-pathogenic microorganisms in the flora of the human body as well as that between the microflora and the host represents a delicate equilibrium. It is well recognized that this eco-system can be easily disarranged by antibiotic treatment, occasionally leading to severe consequences for the host (1, 2, 3). Two types of problems may arise in this respect — the occurrence of superinfections and the emergence of antibiotic resistance among the bacteria.

Resistance factors (R-factors) in bacteria represent one class of plasmids, i.e. genetic elements separate from the bacterial chromosome. They carry genes coding for resistance towards one or several antibiotics. It is now realized that the efficient transfer of such resistance plasmids represents the most important mechanism by which drug resistance is propagated among clinical isolates of bacteria (4). Hence, the emergence of microorganisms carrying resistance plasmids as a result of antibiotic treatment is probably the main cause of the establishment of a multiple resistant microbial flora in man (5, 6, 7). The drug-resistant strains, however, tend to disappear from the microflora of the patient within months after termination of therapy (7), although carriage of antibiotic resistance due to plasmids has occasionally been observed for longer periods (8).

The therapeutic problems caused by resistance plasmids are still moderate among outpatients. However, in hospitalized patients selection of drug-resistant strains is highly undesirable. Luckily, there is no proven correlation between increased virulence and the presence of resistance plasmids in bacteria.

The microorganism most often discussed with regard to the etiology of acne, *Propionibacterium acnes* (P. acnes), is highly susceptible to most antibiotics (9). However, in this presentation we will restrict ourselves to the ecological problems connected with the antibacterial agents most often used in acne therapy, namely tetracyclines, cotrimoxazole, erythromycin, and clindamycin.

## TETRACYCLINES

These agents can inhibit aerobic as well as anaerobic gram-positive and gram-negative bacteria.

Today about 50% of healthy persons in Sweden harbour tetracycline resistant strains as part of their gram-negative intestinal flora (10). When oral tetracycline therapy is started, the resistant strain(s) will dominate the gram-negative flora within a few days, even if small doses such as 0.1 g per day are given (11). Eventually, during continued therapy the carrier rate of gram-negatives resistant to tetracycline and often several other drugs as well, may approach 100%. The selective effect of the highly absorbable tetracycline derivative, doxycycline, is comparable to that of earlier tetracyclines (12). Strains of anaerobic intestinal organisms have also acquired tetracycline resistance. Thus, a high percentage of isolates of the common anaerobe *Bacteroides fragilis* are now reported to be tetracycline resistant (13, 14). This might be one of the reasons, why diarrhoea due to tetracycline therapy is usually mild and transient and severe problems due to microbial overgrowth are rare.

Similarly, gram-positive bacteria such as the beta-hemolytic streptococci have acquired a high degree of tetracycline resistance, although they have preserved their extraordinary susceptibility to penicillins. Today some hospitals report that 50% of the streptococci isolated in different wards are tetracycline-resistant, a frequency that used to be typical for isolates from dermatology patients. Also among isolates of *Micrococcaceae* an increase in resistance due to tetracycline therapy has been observed (15, 16).

Thus, the emergence of bacterial resistance has greatly limited the clinical effectiveness of tetracyclines. There is, however, no evidence to support the concept that the use of tetracycline in acne patients has significantly contributed to this unfavourable situation. Instead, we believe that the frequent use of tetracyclines e.g. in respiratory tract and other infections, for prophylaxis in abdominal surgery and in veterinary medicine (as a growth promotor, for prophy-

laxis or therapeutically) are more important in this respect.

According to several authors tetracycline resistance is not a problem in *P. acnes* species (14, 17). Since side-effects from tetracycline are rare and since the broad spectrum of these drugs now is largely lost, it is our opinion that tetracyclines may continue to be the first choice in the treatment of severe acne. However, in pregnancy tetracyclines should not be used and in patients with recurrent bacterial infections the potential hazard of a multiple resistant flora should be taken into account.

## TRIMETHOPRIM — SULPHAMETOXAZOLE (CO-TRIMOXAZOLE)

This combination of agents possesses a broad activity against gram-positive and gram-negative bacteria. The side-effects are usually rare and include mild intestinal disturbances, sulphonamide allergy, and antifolate depression of blood cell development.

Despite the fact that co-trimoxazole has rather poor activity against anaerobic bacteria *in vitro* as well as clinically and the fact that strains of *P. acnes* range between moderately sensitive and highly resistant, clinical efficacy of co-trimoxazole in acne has been reported (18, 19). Thus, Nordin et al (19) found that 75% of acne patients refractive to tetracycline therapy improved during co-trimoxazole treatment despite the rapid emergence of resistance among skin staphylococci and a constant finding of co-trimoxazole resistant *P. acnes* during the trial in 30% of the patients.

Plasmid-mediated sulphonamide resistance is as common as that against tetracyclines and although trimethoprim is a fairly recent addition to our therapeutic armament low frequencies of plasmid-mediated resistance to this drug are now reported in gram-negative bacteria (20, 21). Co-trimoxazole is widely used e.g. in the treatment of urinary tract infections and bronchitis. Therefore, except in the individual acne patient treated with co-trimoxazole, such usage of the drug would probably have a limited effect on the general emergence of bacterial resistance.

## ERYTHROMYCIN — LINCOMYCIN — CLINDAMYCIN

The activity of these drugs includes gram-positive aerobes and most anaerobes. Clindamycin, which has been most recently introduced, has the broadest spectrum of activity. In mycoplasma infections, in whooping cough, and in various respiratory tract infections in patients allergic to penicillin, erythromycin is usually considered the drug of choice. Due to a fairly restrictive use in Sweden, resistance to erythromycin occurs only in a few percent of clinical isolates. However, resistance towards erythromycin is currently rather common in *Staphylococcus epidermidis*, an organism which may play an indirect role in acne by contributing to the anaerobic milieu necessary for *P. acnes*. Such resistance has been observed in about 20% of strains isolated in our laboratory.

It is well known that resistance towards erythromycin emerges easily when this drug is frequently used. Whether this process can occur also in *Mycoplasma pneumoniae* is not known. Resistance to erythromycin is most often determined by plasmids which sometimes mediate resistance also to unrelated drugs, such as chloramphenicol and tetracyclines. Another important feature of erythromycin resistance is the frequent cross-resistance towards lincomycin and clindamycin. This is of particular significance since in Sweden and elsewhere clindamycin is the current drug of choice in severe anaerobic infections and in severe staphylococcal infections in patients allergic to penicillin.

From our point of view, clindamycin therapy in acne is an even less attractive alternative than erythromycin. Apart from the risk of resistance to a valuable drug which might develop with similar ease as in the case of erythromycin, clindamycin is more than any other antibiotic associated with a potentially fatal pseudomembranous colitis probably caused by an enterotoxin produced through an overgrowth by *Clostridium difficile* (1, 2). Although severe side effects of clindamycin have not been reported in low-dose acne treatment so far (17), we think that the use of clindamycin on a large scale should be minimized.

## CONCLUSION

It is clearly evident from the above discussion that a restricted use of antibiotics is always desirable. It should not be denied, however, that acne may cause problems justifying antibiotic therapy. From a general bacteriological point of view we then suggest that the antibiotics currently used in severe acne should be ranked as follows:

1. Tetracycline, drug of choice
2. Co-trimoxazole, primary alternative
3. Erythromycin, second alternative
4. Clindamycin, third alternative

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## DISCUSSION

*Zachariae, Aarhus:* Well, I would just add that our bacteriologists at home constantly tell us that they would prefer that we use erythromycin and tetracycline. How is it with R-factors in erythromycin? Are they developed to any extent?

*Holm, Umeå:* Resistance towards erythromycin is commonly seen in gram-positives after erythromycin therapy and plasmids seem to be the main basis of resistance.

*Juhlin, Uppsala:* To the same degree?

*Holm, Umeå:* Tetracycline resistance is found both in gram-negatives and gram-positives whereas erythromycin resistance only develops in the latter group, since gram-negatives are inherently resistant to erythromycin. On the other hand, you have the problem with the cross-resistance between erythromycin and clindamycin, and we definitely need to save clindamycin for severe infections.