Characterisation of Antibiotic-resistant Propionibacterium Acnes from Acne Vulgaris and Other Diseases

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Cristina Oprica (*left*) defended her thesis on 2 June 2006 at the Section of Clinical Bacteriology and the Section of Dermatology and Venerology, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm. The external examiner was Professor Brigitte Dreno (*right*), Department of Dermatology, Nantes and the chairman of the reviewing board was Professor Carl Erik Nord.

Propionibacterium acnes is an anaerobic, Gram-positive bacterium that belongs to the normal microflora. The skin is the major habitat but it can also be isolated from other body regions. *P. acnes* plays an important role in the pathogenesis of acne vulgaris. It is very resistant to phagocytosis and can persist intracellularly within macrophages for a long time, which provokes an ongoing immune reaction and long-standing inflammation. The reason may be related to the cell wall structure. The *P. acnes* persistence in tissue may explain the longevity of inflammatory acne. The general perception was that *P. acnes* is a microorganism with low virulence, but during the last years the prevalence of severe, life-threatening infections caused by *P. acnes* has increased especially in immunocompromised patients and in those with prosthetic devices.

P. acnes is the major objective of using antibacterial treatment, which can be administrated either topically or systemically, even though the reduction in bacterial numbers does not correlate to the clinical efficacy. Successful acne treatment with antimicrobials reduces the number of propionibacteria but do not completely eliminate the bacteria from the skin; and the reduction is temporary.

Long courses of antibiotics have been a mainstay of acne treatment. The consequence has been the development of antibiotic-resistant *P. acnes*. Reports about *P. acnes* resistance collected from acne patient were published from many regions of the world. It has been demonstrated that between 1991 and 1997 the proportion of patients carrying resistant bacteria in UK doubled: consequently 60% of patients in Leeds region were found to carry resistant strains. The decrease of colonization rates during late 1998 and 1999 may be explained by a change in prescribing practices due to publicity about development of serious effects. However during 2000 resistant rates started to increase again.

The general aim of the study was to perform a characterisation of *P. acnes* antibiotic-resistant clinical isolates from acne patients and from various diseases. The resistance patterns, epidemiological relatedness and molecular resistance mechanisms have been studied.

In Paper I we found that antibiotic treated acne patients in Stockholm have had a significantly higher risk

of carrying resistant *P. acnes* strains than acne patients who did not receive such treatment. Furthermore, in Paper II we have demonstrated that antimicrobial resistance has emerged among *P. acnes* strains isolates from different severe, life threatening infections in Europe. The bacterial resistance in *P. acnes* clinical isolates from various diseases mirrors the situation with the antimicrobials presently in use in different countries.

We have developed a new pulsed-field gel electrophoresis protocol as typing method for *P. acnes* strains. Pulsed-field gel electrophoresis is a powerful tool in epidemiology for the determination of clonal identity of bacteria. We have demonstrated that antibiotic-resistant *P. acnes* population is polyclonal and skin isolates do not represent a separate pulsed-field type when compared with the bacterial population from other sites than the skin. It was shown that acne patients may be colonized with different *P. acnes* strains with various resistance phenotypes. This finding may suggest that certain bacterial clones are more prone to acquire resistance against a specific antibiotic.

In Paper III we have demonstrated that the resistant strains from acne and other diseases showed well-known mutations in the 23S rRNA and 16S rRNA but also new mechanisms of resistance have evolved. It is conceivable that mobile genetic elements have developed, carrying resistance genes which can be transferred to pathogenic bacteria.

In Paper IV it was shown that oral treatment of acne patients with tetracycline combined with a topical retinoid proved to be a good alternative to isotretinoin regardless of the presence of antibiotic-resistant *P. acnes* on the skin, although patients treated with isotretinoin had a prolonged remission after treatment. The anti-inflammatory properties of the tetracycline could be important in the treatment of inflammatory acne. There is a complex relationship between antibiotic resistance and outcome in acne vulgaris. Numerous factors may influence the follicular antibiotic concentration and it is still an open question how much of the antibiotic efficacy in acne is due to the anti-propionibacterial or anti-inflammatory effect.

The resistance seems to move from the acne patients to the community. In Paper V we have shown that carriage of resistant *P. acnes* isolates occurs not only in acne patients and their close contacts but also in the general population. Close contacts within families were found to carry the same clonal type of antibiotic-resistant *P. acnes* as acne patients.

Acne is one of the very few diseases in which long antibiotic treatments are recommended. Dermatologists treating acne patients should evaluate which is the best treatment for the patient or for the community and consider the antibiotic resistance problem not only in proponibacteria but also in the normal microflora. The cost of resistance may be ameliorated by compensatory mutations causing the stabilization of the antibiotic-resistant bacterial population. It may be possible that certain clonal types have increased capabilities to survive. Efforts should be made in preventing resistance development and accumulation of antibiotic resistant *P. acnes*. The non-antibiotic treatment should therefore be considered as the first alternative in mild to moderate acne and isotretinoin should be appropriately prescribed in acne to prevent physical and psychological problems. Nowadays experts focus on combination therapy that targets more pathogenical factors and may enhance the efficacy

List of publications

I. Oprica C, Emtestam L, Lapins J, Borglund E, Nyberg F, Stenlund K, Lundeberg L, Sillerström E, Nord CE. Antibiotic resistant Propionibacterium acnes on the skin of patients with moderate to severe acne in Stockholm. Anaerobe 2004; 10: 155–164.

II. Oprica C, Nord CE. European surveillance study on antibiotic susceptibility of Propionibacterium acnes strains. Clinical Microbiology and Infection 2005; 11: 204–213.

III. Oprica C, Löfmark S, Lund B, Edlund C, Emtestam L, Nord CE. Genetic basis of resistance in Propionibacterium acnes strains isolated from diverse types of infection in different European countries. Anaerobe 2005; 11: 137–143.

IV. Oprica C, Emtestam L, Hagströmer L, Nord CE. Clinical and microbiological comparisons of isotretinoin versus tetracycline in acne vulgaris. Acta Derm Venerol 2007; 87: 246–254.

V. Oprica C, Fang H, Emtestam L, Nord CE. Carriage of antibiotic resistant Propionibacterium acnes by close contacts of acne patients and healthy volunteers. Manuscript.