PROPIONIBACTERIUM ACNES AND ANTIBIOTIC RESISTANCE – IMPACT ON PUBLIC HEALTH

Acne represents a chronic inflammatory disease, very frequent in adult persons and with a big impact on the patient’s quality of life. Propionibacterium acnes (P. acnes) is involved in acne pathogenesis and its eradication requires treatment with antibacterial substances, especially antibiotics. The use of antibiotics in acne was associated with the development of P. acnes resistance to antibiotics and the possibility to transfer the resistance factors to other bacterial species. In this paper we present the main causes responsible for the development of antibiotic resistance and the measures to prevent it.

Keywords:
acne, Propionibacterium acnes, antibiotic resistance, public health, P. acnes resistance to antibiotics

Abstract

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Cuvinte-cheie:
acnee, Propinibacterium acnes, rezistență la antibiotice, sănătate publică, rezistența la antibiotice a P. acnes,

Rezumat

Acneea reprezintă o afecțiune inflamatorie cronică, frecventă la persoana adultă și asociată cu un important impact negativ asupra calității vieții pacienților. Propionibacterium acnes (P. acnes) este implicat în patogenia acneei și necesită un tratament antibacterian, în special cu preparate antibiotic. Utilizarea preparatelor antibiotică în acnee a fost asociată cu posibilitatea dezvoltării rezistenței lui P. acnes la antibiotice și cu transferul factorilor de rezistență la alte specii bacteriene. În acest articol prezentăm principalele cauze care au condeus la dezvoltarea rezistenței lui P. acnes la antibiotice precum și măsurile care se impun pentru prevenirea instalării rezistenței la antibiotice.
Introduction

Acne is a chronic disease, which requires adherence to the treatment in the long-time management [1,2]. Antibiotics represent an important option in acne treatment for many clinicians [3, 4], and because acne has the characteristics of a chronic disease, [5, 6, 7], the treatment strategy must comprise on a combination of attack treatment and maintenance therapy [8].

Propionibacterium acnes (P. acnes) plays an important role in the pathogenesis of acne vulgaris [8, 9, 10]. P. acnes, previously classified as Corynebacterium parvum, has been implicated in the pathogenesis of acne for more than 100 years, starting with Unna [11] in 1896.

Antimicrobial resistance is a major problem and is an important issue to consider in acne treatment [12] and is a significant public health issue [13]. The main contributors in the development of antibiotic resistance are the pharmaceutical industry, the agriculture, and animal husbandry industry, patients, and healthcare providers [14].

The importance of antibiotic resistance is highlighted by Financial Times [15], respectively „With increasing urgency, national and international health authorities are calling for physicians to limit antibiotic use”.

History of P. acnes resistance to antibiotics

The development of resistance to antibiotics is a direct result of use and abuse of antibiotics [16], and unfortunately the antibiotics use in acne treatment lacks bacterial specificity and has an important risk to generate resistance to antibiotics bacteria [17]. In the last few decades Propionibacterium acnes (P. acnes) has become resistant to many different antibiotics, making them less efficacious in treating acne. A paper from 1976 [20] showed that in more than 1000 patients with acne there was no evidence of antibiotic resistant P. acnes, and it was believed that P. acnes is incapable of developing antibiotic resistance.

But, shortly after the introduction on the market of topical formulations of erythromycin and clindamycin, P. Acnes’s resistance to antibiotics was first noted [21]. In 1979, Crawford [22] reported the first indication of resistance to topical antibiotics in acne, and in the eighties P. Acnes was reported to be resistant to tetracycline [23].

Impact of P. acnes resistance to antibiotics

The most important issues regarding P. Acnes’s resistance to antibiotics are represented by the mechanism of resistance, the prevalence of resistance induction, the role of topical and systemic antibiotics, and the persistence of resistance after the antibiotics are stopped. In respect of the topical antibiotics, the resistance induced is limited on the treated area but with oral antibiotics, the resistance can develop in all body area [24]. The effects of antibiotic resistance of P. Acnes in patients with acne are represented by a reduction of clinical response to antibiotic therapy, a potential increase of P. Acnes pathogenicity and, a multidisciplinary implication, the possibility of resistance transfer to other pathogenic organisms [25].

The presence of P. Acnes resistant to antibiotics will have an important effect and impact on treatment outcome [26, 27], respectively reduced response or no response or relapse shortly after the treatment [23, 26, 27]. Presence of P. Acnes resistant to clindamycin, erythromycin and cyclines is strong connected with no clinical response or frequently relapses after the treatment [22, 28, 29].

According to [30], respectively a systematic review of 50 clinical trials with topical antibiotics, there is a gradual decrease of efficacy of topical erythromycin in acne (both on inflammatory and non-inflammatory lesions), probably connected with the development of antibiotic resistance of P. Acnes.

Another problem [31] with P. Acnes resistance to antibiotics is represented by the implications for other infections, respectively the possibility of transmission of factors conferring resistance to other bacteria [26, 32]. Topical or oral antibiotics for acne treatment used for a long period can select or transfer resistant genes to staphylococci and / or streptococci [22, 33].

One neglected problem in treating acne patients with antibiotics is represented by the patients’ contacts, respectively Miller et al. [34] showed that contacts of acne patients being treated with antibiotics demonstrate significant increased prevalence and density of resistant strains of coagulase-negative Staphylococcus (CNS) compared to those with no contact with acne patients.

This problem can be the direct result of development of resistant coagulase-negative staphylococci (CNS) on both local and distant anatomical sites in patients with acne treated with topical erythromycin [26, 35, 36], and CNS has been shown to transfer resistance to the more pathogenic S. aureus [37].

The modalities of dissemination are represented by person-to-person contact and the spreading of resistant strains can be carried out by the treating physician, family or friends [38, 39, 40]. An important issue is related with the persistence of antibiotic resistance of P. Acnes after the antibiotic treatment is stopped, and the data are divergent, respectively some authors suggest that resistant isolates disappear after antibiotic treatment is stopped [41], other data suggest that resistance persists and can be reactivated rapidly [42].

An alarming fact is represented by an increasing number of reports of systemic infections [43] caused by resistant P. Acnes in non-acne patients (e.g. post-surgery) and this is another side effects of P. Acnes resistance to antibiotics.

Factors associated with P. Acnes resistance to antibiotics

The percentage of acne patients carrying P. Acnes strains resistant to these antibiotics is increasing worldwide and vary from one region to another [31, 40, 44, 45, 46, 47, 48, 49], and probably the main reasons regarding the differences among different...
countries are connected with the prescription of different antibiotic habits and/or different ethnicity of the patients [31].

Countries with higher rates of oral antibiotic use (prescribing practice) for acne had significantly higher rates of resistance of P. acnes [40] and resistance to commonly used antimicrobial drugs is remarkably higher in countries where antibiotics are not restricted [50]. Severity of acne and sales of antibiotics are other factors involved in development of P. acnes resistance to antibiotics, respectively resistance is more frequent in patients with moderate-to-severe acne and in countries with high outpatient antibiotic sales [43]. About the possibilities of acquiring of antibiotic resistance, the authors describes two modalities: for long time and/or contact with people which already have resistant strains [51, 52]. The fact that a lot of patients are already colonized with resistant P. Acnes before starting any acne therapy, is a valuable proof that resistant strains can be transmissible via human-to-human contact [40], possibly among family and friends. An alarming fact is represented by the existence of resistant strains of P. acnes in younger siblings and children of patients with acne [56] and the implication to have resistant strains of P. acnes colonizing the face (25 of 39 tested) [40].

Topical erythromycin and topical clindamycin (the most commonly used in acne) are the main “culprits” for antibiotic resistance of P. acnes [23, 53, 54, 55, 56]. Monotherapy with topical antibiotic should be prohibited because resistant P. acnes strains have been shown to emerge after only 8 weeks with the number of resistant strains increasing progressively if the treatment is continued [57]. Other factors which can be connected with the possibility of developing the antibiotic resistance are previous treatment [41, 40, 27], the amount of a given antibiotic used [58, 59] and prescribing practices [39, 40]. The probability of P. acnes resistance increases with the patient's age, duration of acne, and duration of treatment with topical or systemic antibiotics [51]. Ross et al. [39] showed that the mechanism involved in erythromycin and clindamycin resistance is connected with four phenotypes with cross-sensitivity to macrolide, lincosamide and streptogramin B (MLS) antibiotics. Genetic mutations occur mainly in 23S rRNA, and strains that possess the erm (X) resistance gene are highly resistant to MLS antibiotics. Mutations in genes encoding 23S and 16S represent the molecular basis of resistance, and are widely distributed [39]. In contrast, additional resistant strains without these mutations have also been identified and the mechanisms underlying their reduced antibiotic susceptibility remain to be elucidated [39, 61]. Resistance to clindamycin develop in other ways, with the most common being the bacterium changing the binding site [62, 63].

On the other hand, tetracycline resistance is associated with a single G-C transition in the 16 S rRNA of the small ribosomal subunit [64] and there is an association between resistance to tetracycline, doxycline and minocycline [39].

**How can we prevent the antibiotic resistance?**

The strategies and guidelines for the limitation of antibiotic resistance [58] will change the prescribing practice (the levels of resistance is strongly correlated with the levels of antibiotic use) and will prevent transfer of resistance factors to other bacteria.

According to 2012 European guidelines, oral antibiotics should be used for inflammatory acne only during the induction phase and then discontinued during a maintenance phase with topical therapy [21]. The main objectives of the guidelines are improvement in the care of acne patients, reduction of serious conditions and scarring, promotion of adherence and reduction of antibiotic resistance. Pathogenesis of acne is complex and multifactorial and a combination of different classes of drugs is the best practical approach. The most useful combination, targeting the growth of P. acnes inflammation and comedogenesis, is represented by antibiotics WITH retinoids [66, 67].

Because the antimicrobials and topical retinoid have complementary mechanisms of action, the combination will have a greater efficacy in reducing number of inflammatory and non-inflammatory lesions compared to monotherapy [68, 69, 70, 71]. Another advantage is the fact that patients on combination therapy show faster signs of improvement [72, 73, 74] and the quicker onset of action is connected with better adherence and will reduce the amount of antibiotic exposure and risk of P. Acnes resistance. We must not forget that poor outcome of treatment may be caused by poor adherence [75, 76].

Rates of adherence with acne treatment are higher in adult females, compared with both males and adolescents [77] and the main factors involved in adherence are patient education, use of combination therapies, patient satisfaction, response to treatment and side-effects. In order to have a better adherence we must simplify treatment regimens, decrease doses per day and number of medications used, use medication reminders, following up by phone, encourage patients to join support groups and educate patients during the consultations [78, 79]. Benzoyl peroxide (BPO) has been used since the 1930s due to its antibacterial, keratolytic, and comedolytic properties [80, 14] and is a broad-spectrum antibacterial agent that comes in many formulations and works through the interaction of oxidized intermediates with various constituents of microbial cells [81]. Very important, until now (despite its widespread use) bacterial resistance has not been reported. Topical benzoyl peroxide or azelaic acid may be added to antibiotic therapy to reduce the potential for developing P. acnes resistance [55]. The combination benzoyl peroxide plus a topical retinoid is often used in conjunction with antibiotics to prevent or eliminate the development of antibiotic-resistant P. acnes [82]. The combination of BPO with clindamycin or erythromycin...
is more effective than monotherapy at reducing P. acnes growth (83, 84) and decreases the risk of resistance (85, 57), and the washing with products containing BPO effectively reduces P. acnes, (85, 84) including resistant populations (87). BPO and systemic antibiotics should be used in combination with a topical retinoid, since retinoids target acne precursor lesions (microcomedones) and have a significant effect on comedones (55).

Retinoids do not contribute to antibiotic resistance and are a part of eco-responsible acne treatment (85, 38, 88). Combination therapy involving a topical retinoid plus an antimicrobial is the recommended first-line approach and numerous clinical studies showing improved efficacy of this approach (58, 55). By tailoring the choice of antimicrobial and duration of antibiotic use, the combination topical retinoid plus an antimicrobial can be used for almost all patients with acne, providing results that are faster and superior to antibiotic therapy alone (6, 55). Combination therapy is likely to have a more significant effect because it targets 3 major areas of acne pathophysiology: P. acnes proliferation, inflammation, and hyperkeratinization (55), and topical retinoids are also first-line agents for maintenance therapy (39). Combination therapy aimed at eradicating P. acnes, normalizing the abnormal desquamation of the follicular epithelium, thereby eliminating the environment that supports bacterial proliferation, and controlling the formation of the microcomedo which in turn will prevent formation of new inflammatory acne lesions and comedones (85, 57). Current recommendations also include limiting the duration of systemic antibiotic use, avoiding the use of topical and systemic antibiotics together, adding BPO to retard emergence of resistant bacteria, including a topical retinoid to improve outcomes and using topical retinoids for maintenance therapy adding BPO if needed (40). „The Global Alliance to Improve Outcome in Acne Group recommended the following strategies to limit the development of resistance of P. acnes which included:

1. combine a topical retinoid plus an antimicrobial;
2. limit the use of antibiotics to short periods and discontinue when there is no further improvement or the improvement is only slight;
3. co-prescribe a benzoyl peroxide-containing product or use as washout;
4. oral and topical antibiotics should not be used as monotherapy;
5. concurrent use of oral and topical antibiotics should be avoided, particularly if chemically different;
6. do not switch antibiotics without adequate justification;
7. use topical retinoids for maintenance therapy, with benzoyl peroxide added for an antimicrobial effect if needed;
8. avoid use of antibiotics for maintenance therapy (39).

The current consensus is that topical antibiotics alone should not be used as monotherapy in acne because of their relatively slow onset of action and their potential for causing bacterial resistance (55).

The duration of antibiotic therapy and its effects have not been widely studied (97, 98, 99, 92, 93), and a consensus group suggested limiting the duration of oral antibiotics (55) (oral antibiotics will be used for 3 months and then discontinued when there is good clinical improvement) and that this “acute” treatment must be sustained by topical maintenance therapy (39). Other recommendations of recently published guidelines suggest that the duration of antibiotic therapy can be limited to 3 to 6 months (21, 82, 94, 90). Other recommendations in order to prevent development of antibiotic resistance include stricter cross-infection control measures when assessing acne in the clinic and combining any topical/systemic antibiotic therapy with broad-spectrum antibacterial agents, such as BPO (58, 40, 90).

**Conclusions**

Success against antimicrobial resistance requires an interdisciplinary approach, with increased microbial surveillance, judicious use of antimicrobials not only in human medicine but in agriculture and animal husbandry also, increased research on the biology of microbes and mechanisms of resistance; development of novel antibiotics and vaccines as well as rapid, point-of-care diagnostics; and, most importantly alteration of old prescribing habits (14, 97). Acne lesions typically recur for years, and so acne is nowadays considered to be a chronic disease (39), and the correct approach is attack therapy followed by maintenance therapy.

Maintenance therapy can be defined as the regular use of appropriate therapeutic agents to ensure that acne remains in remission (21). For a successful long-term treatment, any acne maintenance therapy must be tolerable, appropriate for the patient’s lifestyle and convenient. The natural history of acne suggests that maintenance therapy should continue over a period of months to years depending upon the patient’s age (21). Therapy is therefore tailored to the individual patient depending on the nature and severity of their acne (98, 99). In the present era of increasing antibiotic-resistance, it is essential that dermatologists and family physicians treating acne patients be vigilant in prescribing antibiotics (21), and all patients should be informed about the specific risks associated with any given topical and/or systemic therapy (21).

**Acknowledgement**

This paper is supported by the Sectorial Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by Romanian Government under the contract number POSDRU/159/1.5/S/137390.

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