**Propionibacterium acnes and bacterial resistance**

**Propionibacterium acnes e a resistência bacteriana**

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**ABSTRACT**

Propionibacterium acnes (P. acnes) is one of the main microorganisms found on the skin. It is predominantly found in hair follicles, prefers anaerobic conditions, preferably colonizes the areas with high sebum production, and is the main bacterium involved in the pathogenesis of acne. The indiscriminate use of antibiotics for the treatment of acne vulgaris can result in the development of bacterial resistance. The present article is aimed at updating dermatologists with the most current data – from the classification to the physiopathogenic mechanisms involved in bacterial resistance to P. acnes and its possible clinical implications.

Keywords: Propionibacterium acnes; drug resistance, bacterial; acne vulgaris

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**RESUMO**

O Propionibacterium acnes (P. acnes) é um dos principais microrganismos observados na pele. Encontrado predominantemente nos folículos pilosos, prefere condições anaeróbicas, coloniza preferencialmente as regiões com alta produção de sebo e é a principal bactéria envolvida na patogênese da acne. O uso indiscriminado de antibióticos para o tratamento da acne vulgar pode causar o desenvolvimento de resistência bacteriana. Este artigo tem a intenção de fornecer ao dermatologista os dados mais atuais desde sua classificação até os mecanismos fisiopatogênicos envolvidos na resistência bacteriana do P. acnes e suas possíveis implicações clínicas.

Palavras-chave: Propionibacterium acnes; farmacorresistência bacteriana; acne vulgar

**INTRODUCTION**

Propionibacterium acnes (P. acnes) is a gram-positive, facultative anaerobic, diphtheroid-type, non-spore forming bacillus. This bacterium is part of the skin’s microbiome and has a confirmed presence in the stratum corneum and pilosebaceous units. P. acnes contributes to half of the skin’s microbiome, with an estimated density of $10^2$ to $10^6$ clones per square centimeter. In the skin, its distribution is prevalent in the facial and scalp areas, and is related to the high concentration of pilosebaceous units in these sites. It is common in areas rich in eccrine sweat glands and mucous membranes, however it is also present in small amounts in the lower limbs. This agent is also part of the microbiome of the conjunctiva, outer ear, oral cavity, and upper respiratory tract. It can be occasionally commensal in the peripheral lung tissue and mediastinal lymph nodes.
**P. acnes** was previously called *Corynebacterium acnes*, in reference to its ability to ferment carbohydrates into propionic acid and light chain fatty acids (LCFA) – substances with known antimicrobial activity. Lipids and fatty acids, as well as pantetheine, nicotinamide acids are the main sources of nutrition for this bacterium, in addition to some other elements such as cobalt and iron that make up the diet.10

*P. acnes* is known for contributing to health by inhibiting the invasion of the skin by common pathogens such as *Staphylococcus aureus* and *Streptococcus pyogenes*.11 The hydrolyzation of triglycerides with the release of free fatty acids contributes to the acid pH of the skin’s surface, which is another well-known factor for skin protection.12 Fermentation of glycerol has proven to have *in vitro* and *in vivo* probiotic action, suppressing the growth of the USA 300 methicillin-resistant *Staphylococcus aureus*, one of the most prevalent strains in the community.11

The *P. acnes* genome encodes all the key components for the oxidative phosphorylation and has the genes for the cytochrome c oxidase, which ensures its ability to grow in different metabolic conditions.13-15 Thus, *P. acnes* is able to “tolerate” exposure to oxygen for a few hours and survive *in vitro* for up to eight months under anaerobic conditions.16 Many of its genes have recognized virulence factors, conferring pathogenic potential to this bacterium.17

**P. acnes GENETIC CLASSIFICATION**

The sub-classification of *P. acnes* was introduced by Johnson and Cummins with the demonstration of two distinct phenotypes of this agent (Type I and Type II), based on studies of serum agglutination and analysis of the cell wall sugars.18 Subsequently, the phylogenetic analysis of the RecA gene and hemolysin/cytotoxin (tly) of *P. acnes* strains proved different strains of both types.19 Type I was further divided into IA and IB,19, 20 and Subtype III was described.21 Genetic division of *P. acnes* based on multilocus sequence typing technology (MLST), identifies the following subtypes: Type I – IA1, IA2, IB, IC or I-1a, I-1b, I-2, Type II and Type III.22-24

With the sequencing of the *P. acnes* genome (KPA171202, IB strain) the knowledge of this bacterium has further advanced.25 The analysis evidenced a genome of 2.56Mb with 60% GC, encoding 2,333 open reading frames (ORFs), with multiple products such as sildadies, neuraminidases, endoglycoceramides/ endoglycosidases, lipases, and pore-forming enzymes.25 When 82 strains of *P. acnes* had their genomes compared, it was possible to identify concordance in 88% of the genome (2.2Mb). Unique single nucleotide polymorphisms (SNPs) were identified in the central region 122,223, with the possibility of using the ribotyping of the gene 16S in the construction of the phylogenetic tree of *P. acnes* having been demonstrated.26 The non-central genome, which is not shared by all strains, corresponds to 0.90Mb and assists in distinguishing between different strains.26

Combining the knowledge of the bacterium’s genome and the greater ease of use of the technique based on the sequencing of the 16 S rRNA as compared with the MLST technique (the first uses one gene as compared with the second, which uses 6-9), it became possible to define the *P. acnes*’ ribotypes (RT), a fingerprint of the restriction fragments of genomic DNA. The analysis of sixty-nine strains allowed for the identification of the following RTs: 19 RTs1, 5 RTs2, 15 RTs3, 8 RTs4, 7 RTs5, 4 RTs6, 6 RTs8, four strains of smaller RTs, and one III strain.26

On average, each individual has 3±2 *P. acnes* ribotypes, with three or more clones with no difference in the abundance of the bacteria.3 Among the more frequently found ten ribotypes, RT1, RT2, and RT3 were the most prevalent in patients with and without acne. RT4, RT5 (corresponding to the IA-2 class, which is considered an acne-specific subtype) and RT8 were more prevalent in patients bearing acne. RT6 was found only in healthy patients.3, 26, 27

Knowledge of the genetic diversity of *P. acnes* made it possible to understand why a ubiquitous bacterium in humans may be directly related to acne in some individuals and still be critical to the microbiome balance.24, 26

Genomic and proteomic analyses complement the current knowledge when it demonstrates different profiles, with four described proteomic patterns. These patterns also differ according to the conditions of the culture medium, with unique patterns in aerobic and anaerobic conditions, suggesting there is influence of the medium on the bacteria.29

**PATHOGENESIS OF P. ACNES – FACTORS OF VIRULENCE**

*P. acnes* was historically considered an agent of low pathogen potential, however the current knowledge about these bacteria indicates a genetic diversity with different levels of potential for virulence.26

In addition to the single loci 1, 2, and 3 found in RT4 and RT5 (class IA-2) – subtypes associated with acne – a linear plasmid might have a role in the physio-pathogenesis of acne.26 It is predominantly found in acne lesions.20 Genomic loci seem to be originated from mobile genetic elements that encode virulence genes.31 The RT8 strains of IB-1 class, also related to acne, have a single genomic island (20kb locus encoding non-ribosomal peptide synthetases (NRPS), which are possible virulence factors.4

The RT2 strain belongs to Class II and is distributed both in acne-bearing and healthy patients; however RT6 strain prevails in the latter group.3 The most characteristic genetic feature of these strains is the presence of the clustered regularly interspaced short palindromic repeats locus (CRISPR)/Cas systems. The CRISPR/Cas system provides the bacteria with immunity against viruses and plasmids.33 Bacteriophage infections have been associated with the potential pathogenic of bacteria and is also a possible therapeutic agent.34, 35

Type II strains have decreased lipase activity, which is related to the virulence of *P. acnes*.10

Type III strains are rarely found on the skin’s surface.36 There is a loss of 43kb in the length of the genome with 42ORFs of specific genomic property.26 This subtype is related to vertebral disc infection.27, 37
**PATHOGENESIS OF *P. ACNES***

a) Influence of the metabolism

*P. acnes* can be related to the initial stage of acne due to the fact that it causes an increase in the lipogenesis originated in sebaceous glands. It acts through the action of soluble factors or direct action with an increase in the production of 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2) via the cytochrome P450 with increased triacylglycerol synthesis. IGF-1 and IGF-1R are a well-known target of *P. acnes.*

There is also evidence that *P. acnes* influences the differentiation of keratinocytes via an increase in transglutaminase and cytokeratin, and a decrease in the expression levels of cytokeratins 1 and 10. Some strains are even capable of increasing the involucrin, the expression of mRNA of cytokeratin 6, and decreasing the levels of expression of cytokeratin 6 and 16. The effect on keratinocyte differentiation suggests it has influence on the formation of microcomedones.

b) Biofilm

The production of a biofilm by *Propionibacterium acnes* — a glycolcalyx polymer, which acts as a biological glue — was evidenced by genomic studies. The production of the biofilm is closely related to invasive infections and is considered an important factor in these infections, as demonstrated in 93 isolates. The production of biofilm can take place in the follicles and has been reported in patients with acne in whom the substance led to inflammation that was not associated with cellular immune response. When present in the sebum, this polymer leads to the adhesion of keratinocytes, contributing to the formation of comedones. It is believed that this substance has an influence on the immunogenicity, clinical course, and impact on the therapeutic response of acne pictures.

c) Proteases

There is evidence suggesting *P. acnes* has a role in increased expressions of interleukins 1’s and 8’s mRNA, of tumor necrosis factor alpha, of human beta defensin beta 2, and of metalloproteinases 1, 2, 3, 9 and 13 in keratinocytes by activation of proteases, and of proteins activated receptor (protein-activated receptor 2 PAR-2). Metalloproteinases can be related both to the pathophysiology of acne and scar formation.

The Christie, Atkins, Munch-Peterson factor (Camp factor) is a secretory protein with co-hemolytic activity and virulence potential against keratinocytes and macrophages that can be encoded by *P. acnes.* Despite being secreted by *P. acnes,* the specific role of the Camp factor in the pathogenesis of disorders is still unclear.

Endogenous porphyrins can be produced by *P. acnes* with a possible influence on perifollicular inflammation by cytotoxic effect and the stimulus of interleukin 8 production. After the follicle’s rupture and probably by the action of singlet oxygen, the porphyrins can continue their action due to the fact they promote the development of cytotoxic substances, such as squalene peroxide.

d) Inflammation

In patients with acne, *P. acnes* is capable of activating innate immunity via toll-like receptor type 2 (TLR2). This activation occurs via cell wall components of the bacterium, except for when it is not damaged or inactivated. In response to the activation of TLR2, there is production of IL-1α by follicular keratinocytes, (a proven role in the comedogenesis), production of nuclear factor kappa-light (NF-κB, primary transcriptional factor of fast action) by activated B cells, and production of IL-12 and IL-8 by monocytes. When *in vitro,* *P. acnes* is capable of inducing the mRNA of the MMP-9 and MMP-1 and the expression of MMP-9 (but not MMP-1), through a mechanism dependent on TLR2.

The *in vitro* activation of macrophages is accompanied by increased expression of the synthase gene induced by nitrous oxide (inducible nitric oxide synthase – iNOS) and of the cyclooxygenase-2 gene (COX-2), with an increase in nitrous oxide (NO) and of prostaglandin E₂ (PG E²) through a dose-dependent mechanism. This activation was also observed in keratinocytes. In the same study there is evidence of the toll-like pathway, for when TLR-2 are blocked with inhibitory antibodies, the increase in the expression of genes is halted.

Innate immunity can also be activated by pattern-recognition cytoplasmic receptors, and the oligomerization domains, by binding with nucleotides (nucleotide binding oligomerization domain – NOD). These receptors are termed NOD-like receptors (NLK) and assist in the identification of microorganisms and molecules with potential for damaging the cell, such as reactive oxygen species (ROS). When activated by direct binding, the NLR forms a multiprotein complex with adapter proteins and pro-caspase-1, and is then termed inflammasome. Four inflammasomes are described as being capable of identifying bacteria: NLRP1, NLRP3, NLRC4 (also known as IPAF) – all of which belong to the NLR family – and a fourth called AIM2 – that does not belong to this family. Their activation takes place after the cleavage of pro-caspase-1 active caspase-1, the protease that processes the pro-interleukin 1b and 18 into mature and active interleukins.

*P. acnes* activates the NLRP3 on human monocytes. It has been shown that the release of IL-1β by monocytes depends on the phagocytosis of *P. acnes.* Strains with proven ability to invade epithelial cells are of type I in 71% of cases. IL-1β is potentially responsible for the induction of *in vivo* neutrophil inflammatory response induced by *P. acnes.* The bacterium can induce the formation of caspase-1 in neutrophils, with the generation of additional IL-1β and IL-18. The activation of the inflammasome can also activate NF-Kβ. *P. acnes* also induces the production of IL-1 in sebocytes.

*P. acnes* stimulates the production of genes linked to the Th17 immune response, in addition to stimulating the secretion of IL-17 by CD4+ lymphocytes. Vitamin A, and vitamin D are capable of inhibiting the Th17 differentiation induced by *P. acnes.*

With the expanding knowledge about the different *P. acnes* strains and their influence on innate immunity, the identi-
fication of the phylogenetic groups tend to occur not only based on the standard of secreted proteins, but also based on the ability to induce different patterns of immune response. Another important aspect of the inflammatory cascade induced by *P. acnes* is that some are stimulated by dead *P. acnes* or its components, a fact that should be taken into consideration in the acne bearing patient's therapeutic strategy, using substances with bactericidal and anti-inflammatory actions.

Knowledge of the impact of this bacterium on the immune system has allowed the use of this agent in various immunomodulatory strategies, especially in veterinary medicine, as described in the following examples: the inactivated bacteria stimulates Th1 and Th2 response in mice; it is capable of inducing antitumor response, increasing the resistance against viral and parasitic infections, preventing focal segmental glomerulosclerosis; it has antibacterial activity; in murine model of sepsis it reduces the mortality by 50%; it is used in a vaccine that improves the atopic dermatitis murine model, in addition to its use aimed at preventing infections and preparing vaccines.

**Evasion mechanisms**

After having been phagocytized, *P. acnes* can survive and persist within macrophages, interfering or blocking the maturation pathway of phagosomes. *P. acnes* has an intracellular life cycle, offering a possible niche for the survival and spread of the bacteria.

**P. acnes and human diseases**

*P. acnes* has a proven role in acne, however its importance in other diseases is underestimated.

With the ability of growing in medium with diverse oxygenation conditions (in particular in anaerobic settings), of surviving intracellularly in macrophages with the potential to generate inflammation and producing biofilm, *P. acnes* can be transferred from its habitat (e.g. the skin’s microbiome) to deeper tissues, and with the ability to survive and present pathogenic potential. In addition to direct contamination through the skin, infection by *P. acnes* may result from transient bacteremia.

Infections by this bacterium usually have an indolent course and are difficult to diagnose for it is a common bacterium and differentiating contaminations from infections is always a challenge – nevertheless the formation of biofilm is used to differentiate these two clinical situations. In a study with 522 patients, clinically significant bacteremia of *P. acnes* occurred in 3.5% of cases, of which 55.6% were classified as nosocomial, 33.3% had a history of previous invasive procedure and 5.9% mortality.

**Sarcoidosis**

Sarcoidosis is a systemic granulomatous disorder that affects individuals with genetic susceptibility after exposure to a particular environmental stimulus, with *Propionibacterium acnes* being a proven cause. The correlation between the bacterium and sarcoidosis granuloma was demonstrated by techniques of *in situ* hybridization, immunohistochemistry with monoclonal antibodies against *P. acnes*, granuloma based isolation in culture, and the complete sequencing of the sarcoidosis bearing patient's bacterium's genome. A murine experimental model was capable of inducing sarcoidosis granuloma formation after the administration of a recombinant protein from active or dead *P. acnes*. Considering the studies on the influence of *P. acnes* on sarcoidosis, authors have postulated the hypothesis that a hypersensitivity response, with a change in Th1/Th17 balance can generate the sarcoidosis picture. In an interesting case report that identifies *P. acnes* in sarcoidosis granuloma, the patient was treated with clarithromycin with the complete resolution of the condition.

**Prostate cancer**

Recent studies relate the chronic inflammatory state with prostate carcinogenesis due to DNA damage that leads to tissue replication, migration, and angiogenesis. There is evidence of *P. acnes* in prostate tissue with chronic inflammation, verified through techniques of monoclonal antibody, *in situ* hybridization with fluorescence, and immunohistochemistry. The infection's pathway is not yet established, but isolation of *P. acnes* in urine samples suggests the urethra is a possible channel. A murine model of chronic prostatic inflammation was possible after transurethral catheterization of *P. acnes*. Categorizing by type, using the MLST technique, demonstrates that prostate strains do not have a cutaneous origin, contradicting researchers who advocate the possibility of contamination during the collection of prostatectomy material. Vimentin appears to be a key determinant factor for prostatic tissue invasion. Another study correlates *P. acnes* titles with prostate cancer.

**Infection of orthopedic prostheses**

*P. acnes* is one of the agents that causes shoulder prosthesis infection most frequently (second only to *S. aureus*). Despite the small number of the sample, the analysis of 22 shoulder prosthesis infection isolates led to the conclusion that the hemolytic phenotype was the one most associated in this case. This infection's prevalence varies from 3.9% to 15.4% and delayed diagnosis can have an impact on the success of the procedure, with loss of the prosthesis, chronic pain, exudate and sepsis having been described. Spinal prosthetic infections are also related to *P. acnes*, with an incidence of 0.2%, however possibly reaching 12.0% depending on the used instrumentation.

**Endocarditis**

Endocarditis caused by *P. acnes* is rare and is related to heart valve prostheses. There are reports of cases that onset after invasive procedures. Due to the subacute oligosymptomatic development, diagnosis is often delayed, entailing valvular and perivalvar destruction or abscess formation, with mortality rates reaching roughly 18.7%. Little is known about the ideal treatment, and surgery is commonly indicated with an aim at draining the abscess or replacing the valve.
Central nervous system infection

*P. acnes* is related to post-operative infections of the central nervous system, and among common procedures are the use of shunts, bone grafts, craniotomy, abscess drainage, and rare descriptions of meningitis cases with no previous history of procedure (8 reported cases). In half of the cases, symptoms may appear acutely within seven days or subacutely within 14 weeks in the other half, on average. Symptoms are those deemed classic for meningitis, with a cerebrospinal fluid (CSF) profile corresponding to that of the aseptic meningitis with mononuclear pleocytosis. Based on reports, penicillin G, chloramphenicol or vancomycin are used with favorable results. Optic nerve neuritis and abscess formation are described complications.

Other infections

Breast implant infection, acute post-traumatic endophthalmitis, discitis and spondylodiscitis, pericarditis, aortic stent endarteritis, prosthetic eye infection, osteomyelitis, surgical wound infection, endodontic infection and keratitis.

Related dermatological conditions

Progressive macular hypomelanosis of the trunk, alopecia and Sapho syndrome.

*P. acnes* diagnosis

Despite the bacterium having aerotolerant characteristics, the diagnosis of *P. acnes* should be performed in a culture medium with anaerobic conditions – thioglycolate is the routinely used culture medium. When enriched, this culture medium has a low redox potential and assists in the growth of the microorganism.

There should be a systematic subculture on agar plates even in the absence of turbidity. The optimum temperature for growth is 37°C, and the duration of inoculation should be continued for at least 14 days. On the other hand, the culture duration should not be too long, for the probability of contamination by growth of bacteria originating from the normal flora would increase – as a result the maximum waiting period has not been established yet. The interpretation of cultures should be performed with caution, especially if there is only a single medium. For greater reliability of the result, growth should be observed in more than one culture medium, always in light of the correlated patient’s clinical data and, where possible, of other diagnostic methods, such as histology and molecular diagnostics. Fluorescence with *in situ* hybridization (Fish) is a technique with potential use in blood cultures. It showed 95% sensitivity and 100% specificity in the diagnosis of infection by *P. acnes*.

For the isolation and identification of *P. acnes*, attention should be paid to the collection methodology, for different techniques will demonstrate anatomically distinct populations: swab and scraping are used to identify the more superficial bacteria; the use of tape with cyanoacrylate targets superficial and infundibular populations; the punch evidences deeper follicular populations and can be used in biofilm research; finally there are direct tissular visualization techniques, such as the Fish technique, immunofluorescence microscopy and immunohistochemical techniques.

Antibiotic resistance by *Propionibacterium acnes*

The first documented antibiotic resistance by *P. acnes* was linked to erythromycin. The known mechanisms of resistance are: specific mutations to the genes that encode the ribosomal RNA, single mutation in the 16S rRNA (1058G>C) gene, mutations in the gene 23S rRNA with four recognized phenotypic groups (Group I: 2058A> G, Group II: presence of RNA methylase erm(X) gene in a mobile genetic element, Group III: 2057G> A; Group IV: A2059A> G) and mediated erm(X) resistance. Resistance to rifampicin is associated with a punctual mutation in the rpoB gene’s Clusters I and II, and can be prevented if associated with levofloxacin, clindamycin, and penicillin G (Chart 1).

Antibiotic resistance by *P. acnes* is better studied in acne patients. The most significant resistance profiles for the treatment of acne are associated with specific strains of bacteria, in particular ST3 clone, which has worldwide distribution. The ribotypes that are more frequently related to resistance are RT4 and RT5. An individual can host a complex population of *P. acnes*, with a variable number of clones from one to six, which have different pathogen potential and different resistance patterns, issues that directly impact the difficulty in acne treatment. In addition to having the bacteria, a person can transmit the different clones, and thus resistant bacteria can be spread in the population.

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<tr>
<th>Mutation</th>
<th>Resistance</th>
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<tr>
<td>Specific mutation in the gene 165 rRNA (1058G&gt;G)</td>
<td>Tetracyclines</td>
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<tr>
<td>Specific mutation in the gene 23S rRNA (2058A&gt;C)</td>
<td>MSL Antibiotics (macrolide-streptogramin B-lycosamide, including erythromycin and clindamycin)</td>
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<tr>
<td>Presence of the gene RNA methylase erm(3)</td>
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<tr>
<td>Specific mutation in the gene 23S rRNA (2057G&gt;A)</td>
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<td>Specific mutation in the gene 23S rRNA (A2059A&gt;G)</td>
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<td>Specific mutation in the gene 23S rRNA (2058A&gt;T)</td>
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<td>Specific mutation in the gene 23S rRNA (2058A&gt;C)</td>
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<tr>
<td>Specific mutation in the gene rpoB</td>
<td>Rifampicin</td>
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P. acnes and bacterial resistance


There has been an increasing number of cases of antibiotic-resistance by *P. acnes* over the years: in the UK, the resistance rate increased from 34.5% in 1991 to 55.5% in 2000,156 94% of the isolates in Spain and 51% from the isolates in Hungary were resistant to at least one antibiotic.155 The highest resistance rates are related to erythromycin, with cross-resistance to clindamycin. The lowest rates are linked to tetracyclines.157, 158

The evaluation of 114 isolates in Denmark (72 acne bearing and 42 healthy patients) showed 34% of antibiotic resistance by *P. acnes*, with 15.8% resistance to clindamycin, 8.8% resistance to erythromycin, and 9.6% resistance to tetracycline, with 39 patients having been affected: 25 acne bearing patients who had the highest proportion of isolates with resistance to tetracycline.153 In Japan, the rate of resistance to macrolides was observed between 1997-1998 and 2007.165 Prior use of antibiotics (oral or local) was considered a risk factor for resistance, and the use of retinoids, despite its decreasing effect in the growth rate of *P. acnes*, did not influence the incidence of resistant strains.165

Data published in Latin America show a resistance ratio of 33.7% in Chile: 26.3% to trimethoprim-sulfamethoxazole, 12.5% to erythromycin, and 7.5% to clindamycin, with a total cross-resistance between clindamycin and erythromycin, and 40% cross-resistance between erythromycin and trimethoprim-sulfamethoxazole, without identifying resistance to tetracycline and doxycycline.160 The main risk factors for the occurrence of resistance were: older age, previous use of topical antibiotic and, in the case of trimethoprim-sulfamethoxazole, the severity of the acne.160 In Colombia, there were 35% of strains resistant to erythromycin, 15% to clindamycin, 9% to doxycycline, 8% to tetracycline and 1% to minocycline, with 12% cross-resistance between erythromycin and clindamycin, 6% between doxycycline and tetracycline, with previous use of antibiotics being the main risk factor.161

In Mexico there was an 82% resistance to azithromycin, 68% resistance to trimethoprim-sulfamethoxazole, and 46% resistance to erythromycin.162 Elsewhere, in Hong Kong, 54.8% of strains were resistant (53.5% to clindamycin, 20.9% to erythromycin, 16.3% to tetracycline, 16.3% to doxycycline and 16.3% to minocycline), with an 11.6% cross-resistance between clindamycin and erythromycin, and 16.4% of multiple resistors.163 In Egypt, resistance to clindamycin was identified in 66.3%, to erythromycin in 49%, to tetracycline in 26.5%, to doxycycline in 16.3%, and to azithromycin in 9.2%.164 (Table 1).

In Australia, growth in the *P. acnes* resistance rate was not observed between 1997-1998 and 2007.165 Prior use of antibiotics (oral or local) was considered a risk factor for resistance, and the use of retinoids, despite its decreasing effect in the growth rate of *P. acnes*, did not influence the incidence of resistant strains.165

A European study of 304 isolates of *P. acnes* from 13 laboratories in 13 different countries tested six antibiotics.166 Blood was the most common source, followed by skin infections, in soft tissue and abdominal infection.166 Of the isolates, 2.6% were resistant to tetracycline, 15.1% to clindamycin, and 17.1% to erythromycin, without descriptions of resistance to linezolid, benzathine penicillin, and vancomycin.166 There was a variation in the resistance profile among countries, with 83% in Croatia, 60% in Italy, and none in Norway, with blood isolates showing a prevalence among the resistant ones.166

As *P. acnes* has a low susceptibility to cephalosporins, use of antibiotic prophylaxis in surgical procedures (where this bacterium is an important source of post-operative complications) should be revised.167

In cases of severe infections caused by *P. acnes*, drugs with the possibility of resistance cannot be used, and surgical procedures should be associated with clinical treatment, with a preference – when in combination – for using crystalline penicillin, vancomycin, daptoymycin, and rifampicin due to their effect on the biofilm.166, 168, 169
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