

Can We Define Acne as a Chronic Disease?

If So, How and When?

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Abstract

There is widespread misunderstanding of acne amongst both the medical and lay community, who often perceive the condition to be a simple, self-limited affliction of adolescents. Because many think that the disease "will go away on its own," they do not feel an urgency to aggressively treat acne. However, very often the reality is that acne treatment can be quite difficult. Furthermore, acne can be a devastating disease for the patient, since it manifests on visible body parts and in children near puberty, who are vulnerable both socially and psychologically. Most typically, acne is not an acute disease but rather a condition that continuously changes in its distribution and severity. Usually, acne treatment is necessary for many months and sometimes years. Despite treatment, acne may cause scarring and associated negative psychological effects. It is important for both patients and physicians to be aware that very effective treatments are available. It is also important to realize that new studies have proven the benefit of maintenance therapy with topical retinoids; these agents can minimize the potential for relapse, which is part of the natural history of acne. This article reviews the evidence suggesting that acne is a chronic disease in at least a subset of individuals. The members of the Global Alliance to Improve Outcomes in Acne believe that acne should be recognized and investigated as a chronic disease. This will change expectations of clinical trial design and treatment and will highlight gaps in the knowledge of acne epidemiology. The result should be an improvement in patient outcomes.

Although acne is often referred to as a chronic disease, it is seldom viewed as similar to other chronic diseases such as diabetes mellitus or epilepsy. Many see acne as a simple disease, mainly confined to teenagers, which can be readily treated using topical drugs. This may be because of its natural history – acne can spontaneously resolve and quite often presents as a self-limited condition lasting approximately 3–5 years. Yet successful treatment of acne can pose a very real challenge for clinicians. For a substantial group of patients, acne is a devastating, chronic, and frequently relapsing condition; some patients also experience the lifelong sequela of acne scarring. This article by the Global Alliance to Improve Outcomes in Acne discusses the characteristics of acne that define it as a chronic disease and the fact that it is clinically challenging to identify which patients will have a chronic course. The Global Alliance believes that acne needs to be recognized and investigated as a chronic disease, with appropriate expectations in clinical and epidemiologic studies. This is partic-

ularly important because the psychosocial impact of acne may be very long-lasting even in those with self-limited disease.

1. Defining Chronic Disease

Acne can be a long-lasting disease that strikes at various points in a person's life cycle. However, is that enough to consider it a chronic disease? Although many organizations have attempted to quantify chronic disease, standardized definitions are still lacking in many areas. In the US, the Centers for Disease Control state that "a chronic disease is one that, in general terms, has a prolonged course, that does not resolve spontaneously, and for which a complete cure is rarely achieved."^[1]

In 2004, O'Halloran et al.^[2] from Australia reviewed the medical literature and listed the following criteria for a chronic disease:

- duration ≥ 6 months;
- pattern of recurrence or deterioration;

- poor prognosis;
- consequences or sequelae that impact on the individual's quality of life.

The WHO International Classification of Impairments, Disabilities, and Handicaps (ICIDH)^[3] defines acute disease as one that is self-limited either by the course of the disease or by intervention. A classic example of this would be a bacterial or viral infection. According to ICIDH, the term 'chronic' applies to diseases with the following characteristics:

- long-term;
- relapsing;
- non-self-limited;
- may manifest as acute outbreaks, or slow-onset illness;
- wave-like pattern;
- psychosocial impact.

2. Characteristics of Acne that Suggest Chronicity

Acne is one of the most common skin diseases treated in routine clinical care. In the authors' experience, about 60% of patients with acne have a self-limiting condition with few long-term sequelae. This is what both the lay public and medical community typically envision when the term acne is used: pimples and papules that last for approximately 3–5 years. These cases can often be managed with acute treatment followed by a variable period of topical maintenance therapy. Many patients with acne have significant skin pathology and tend to visit their physicians for care very frequently (six or more times per year is not uncommon).^[4,5] One very important point for clinicians is that the psychosocial impact of the disease does not always directly correlate with the number of lesions or severity of disease.^[6] Furthermore, the psychosocial impact may not abate when the disease ceases to manifest.

Acne is also a disease for which there are effective treatments which, in some cases, should be continued for a prolonged period of time.^[7] Even oral isotretinoin, a drug that revolutionized the treatment of severe acne, is administered for a period of 20 weeks and may sometimes need to be given as a second or third course in very refractory disease.^[7] In addition, new studies show that maintenance therapy can minimize the potential for relapse and recurrence.^[8–11] This, in turn, may optimize patient outcomes by reducing the risk of physical and emotional scarring. These studies, which focus on the role of topical retinoids as maintenance therapy through their effect on the microcomedo, represent a departure from the more traditional use of oral antibacterials or nothing as maintenance therapy in acne.^[12]

2.1 The Continuum of Acne

The spectrum of acne encompasses variants that are present at birth as well as types that develop later in life. Previously, prominent acne researchers elegantly outlined proof that acne can affect

neonates, prepubescent children, adolescents, and adults.^[13] Furthermore, when discussing the prevalence of acne amongst early adolescent and adolescent individuals, Kligman^[14] noted that "acne is a continuum, and all members of the population can be placed somewhere along the spectrum." Thiboutot and Lookingbill^[13] note that neonatal acne has its onset and resolution within the first 6 months of life, stereotypical adolescent acne occurs between 8 and 12 years of age and generally resolves by the third decade (but may persist into the fourth and fifth decades), and adult acne encompasses both persistent adolescent acne and new-onset acne in adults who have not had the condition before. Furthermore, these authors suggest that there may be links between the manifestations of acne at different life stages. A small follow-up study of patients with neonatal acne found that those with early acne were more prone to have acne in their teenage years and to have more severe acne compared with control patients.^[13,15] Dreno and Poli^[16] also reported that pre-pubertal acne lesions are associated with a greater risk of severe acne in teenage years and a need for therapy with oral isotretinoin.

2.2 Epidemiology of Acne

Review of the medical literature shows that acne has a mean age of onset of 11 years in girls and 12 years in boys.^[16] In a study of 409 patients, the percentage of patients with acne increased with age during the adolescent years, from 22% of 13-year-old patients to 68% of 16-year-old patients.^[16] Of note, the mean age of onset is different in individuals with darker skin tones, that is, 16 years in Hispanics, 18.9 years in Asians, and 20.3 years in African Americans.^[17] In addition, >70% of patients with skin of color have "chronic active disease," often accompanied by hyperpigmented areas of skin persisting for ≥ 4 months.^[16]

Table I presents the prevalence of acne in more than 2000 individuals (1066 women and 1089 men) aged 18–70 years.^[18] This study showed that clinical acne was more common in men

Table I. Prevalence of acne according to grade and age^[18]

Type of acne	Age range (y)	Male (%)	Female (%)
Clinical ^a	18–28	35	23
	29–39	3	10*
	40–49	3	5
Physiologic acne ^b	18–28	10	25**
	30–34	30	29
	50–59	6	8

a Major acne, ranging from superficial inflamed lesions to nodules and cysts. Data for minor acne and no acne not shown.

b A few lesions seen by the physician but not noticed by the patient (physiologic acne).

* $p < 0.05$; ** $p < 0.01$.

during adolescent years, but more common in women after the age of 23 years.^[18]

Goulden et al.^[19] found that 54% of women and 40% of men aged >25 years had some degree of facial acne, with clinically apparent facial acne being present in 3% of men and 12% of women. In this study, the prevalence of acne declined significantly only after age 45 years. Furthermore, the vast majority of patients with clinically apparent acne (82%) indicated that their condition had been present since adolescence. Poli et al.^[20] found a prevalence of acne in 41% of women in the general population, with a high proportion of late-onset acne. Dreno and Poli^[16] found that among 3305 adult women completing a self-administered questionnaire, clinical acne was present in 17%; about one-third of these women had not experienced acne during their childhood and the majority (78%) experienced premenstrual acne flares. Most recently, Tan^[21] reported baseline demographic data for 619 patients with acne evaluated at dermatology clinics. As shown in figure 1, a large proportion of these patients had long-lasting acne, defined as acne persisting >2 years.^[21] Taken together, these data argue for the chronicity of acne. However, as stated in the introductory paragraph, it remains difficult to predict whether acne will follow an acute or chronic course.

2.3 Outcomes of Acne

The epidemiologic studies reviewed in sections 2.1 and 2.2 underscore the fact that the problems associated with acne are not related only to the 'traditional' self-limited pubertal acne. Indeed, Neimeir et al.^[6] have correctly used the word "impairment," consistent with ICDH nomenclature, to describe the impact of acne. In a recent article, James^[22] stated that acne patients evaluated in a "tertiary care center are prone to depression, social withdrawal, anxiety, and anger and are more likely to be unemployed than persons without acne." Kellett and Gawkrödger^[23] reported that 44% of adult patients with acne had clinically relevant levels of anxiety and 18% had depression. In the same study, female patients were more likely to be significantly embarrassed about their skin condition than male patients, a finding that suggests that women with acne may be particularly susceptible to negative emotional consequences. Acne may also have economic implications; as early as 1986, Cunliffe^[24] showed that unemployment levels in patients with acne were 76% higher in men and 64% higher in women compared with randomly selected control subjects. Acne is common, it is serious, and improved management can make a dramatic difference in many thousands of patients' lives.

Another important outcome of acne is scarring. Goulden et al.^[19] reported that among 361 adults with some degree of facial acne, scarring was present in 14% of women and 11% of men. Most commonly, scars were of the macular atrophic and 'ice-pick' varieties. Dreno and Poli^[16] found that 49% of adult women with

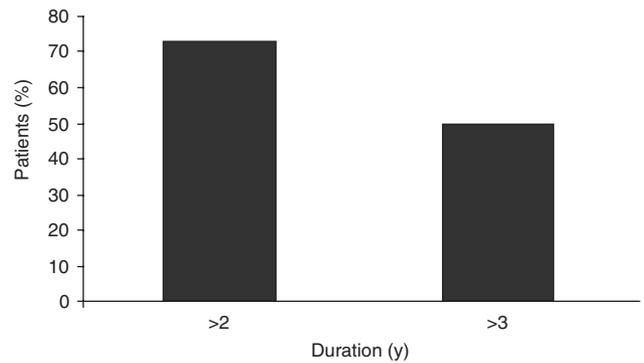


Fig. 1. Duration of acne among 619 patients in the Canadian Acne Epidemiological Survey at baseline.^[21]

clinical acne had sequelae including scarring and/or hyperpigmentation. Acne scarring and hyperpigmentation are managed with a variety of approaches, ranging from chemical peels to laser surgery. However, these treatments can be difficult to tolerate, are often quite expensive, and may not be covered by the patient's health insurance.

The psychosocial and quality-of-life impairments associated with acne can persist over decades, not only in that group of patients whose disease activity persists into adulthood but also as a result of having self-limited severe pubertal acne.^[25-28] This may be as a direct result of persistent physical scarring but also as a consequence of long-term psychological scarring from relatively short-lived but severe disease in adolescence. For example, life decisions relating to relationships and study and work choices taken in teenage years can be influenced by the effects of acne at that time and may have life-long implications for a patient. Teenagers may avoid social contacts because of shame or embarrassment; this may affect dating, participation in school and sports activities, and work. Hypothetically, at least, fewer social activities during teenage years may affect acceptance into higher education programs and less early work experience may have a long-term impact on careers. The presence of visible acne or acne scarring may also affect the opinions of interviewers for higher education or work positions and could therefore also contribute to missed education or career opportunities. The secondary psychosocial effects of acne can, therefore, be chronic even in patients who have time-limited disease.^[25-28]

Table II shows disease outcomes as defined by the WHO.^[3] By this definition, acne is certainly capable of causing impairment, which refers to dysfunction of the body, and affects both the skin and the physis. Chronic acne can encompass the spectrum of disease from mild to severe, and it has long been recognized that acne conglobata and acne inversa are the most disabling and physically distressing types of acne. However, milder forms can also be long-lasting and contribute to significant quality-of-life issues. Disability, defined by the WHO as any restriction or lack of

Table II. WHO International Classification of Impairments, Disabilities, and Handicaps definitions of disease outcomes^[9]

Impairment	Any loss or abnormality of psychological, physiologic, anatomic structure or function. Impairment refers to dysfunction of the body and is concerned with individual function of the parts of the body. This implies that impairments represent disturbances at the organ level
Disability	Any restriction or lack of ability, resulting from impairment, to perform an activity in a manner, or within the range considered being the norm. Disability characterizes the inabilities and is concerned with compound or integrated activities expected of a person or of the body as a whole, such as represented by tasks, skills, and behavior. This implies the disability reflects the consequences of impairment in terms of functional performance and activity by a person. The disturbance is thus at the person level
Handicap	A disadvantage experienced by a person that results from an impairment and/or a disability that limits or prevents the fulfillment of a role that is considered to be the norm (depending on the individual's age, gender, social, and cultural factors). Handicap is thus a broad concept that represents the social and environment results of impairments and/or disabilities for the individual, the family, and society. The disturbance thus represents the interaction and adaptation regarding the cultural, social, economic, and environment consequences for the person

ability to perform an activity in a normal manner, is also therefore a feature of acne.

2.4 Theoretic Causes of Chronic Acne

The reasons why acne becomes chronic in a subset of individuals are not well known. It has been proposed that serum levels of dehydroepiandrosterone sulfate may play a role and that the pilosebaceous follicle is more sensitive to androgenic stimulation in some individuals.^[13] Kligman^[29] suggested that acne in adult women may be secondary to production of stress-related adrenal androgens. There is controversy about whether nutritional factors in Western diets may have contributory effects.^[30-32] Smoking in acne inversa is strongly correlated with activity of the disease; additionally, smoking is associated with an increased frequency of acne in general, with the risk of acne being greatest in young male smokers.^[16,33] Furthermore, women taking contraceptive pills with androgenic activity are more prone to persistent acne (although newer oral contraceptives are associated with an anti-acne effect).^[7,16]

Another theory is that persistence of *Propionibacterium acnes* may play a role in persistent and late-onset acne. Till et al.^[34] found that both adolescents and older patients with acne had higher levels of propionibacteria ($p < 0.05$) than age-matched control individuals without acne. *P. acnes* is known to be a

powerful immune stimulant, and while it is not infectious in acne, it does seem to play a role in triggering disease.^[7]

There have been attempts to discover which patients are more likely to have a chronic course of acne. Goulden et al.^[19] found a very significant correlation between familial background of persistent adult acne and a chronic course (odds ratio 3.93, 95% CI 2.79, 5.51; $p < 0.001$). Other factors that have been associated with a chronic course of acne include severe acne conglobata, keloidal acne, androgenic acne, cases of chloracne, and professional acne.^[35,36] Acne inversa is considered by most dermatologists to be a chronic disease.

2.5 Comparison Between Acne and Atopic Dermatitis

Table III presents a comparison of acne and atopic dermatitis, an accepted chronic skin disease, to illustrate the similar characteristics of these diseases. Both diseases have a strong inflammatory basis and either may have short or very long courses. Both diseases are thought to be influenced by genetic factors, typically with the involvement of multiple genes. In addition, both conditions are characterized by frequent relapse and recurrence, particularly if treatment is discontinued.

The physical and psychosocial impact of both acne and atopic dermatitis can be significant.^[37,38] Several studies have shown that acne is associated with emotional problems such as embarrassment and anger, and can also lead to social withdrawal and limitations in lifestyle.^[39,40] Indeed, the psychosocial impact of acne is similar to those for asthma, seizure disorders, diabetes, and arthritis.^[39,41] It is essential for all clinicians who manage acne to

Table III. Comparison of acne and atopic dermatitis

Parameter	Acne	Atopic dermatitis
Basic character	Inflammatory	Inflammatory
Duration	>3 mo to 5–40 y	>3 mo to 5–40 y
Genetic influence	Yes, particularly with long-term course. Thought to be polygenic	Yes, thought to be polygenic
Age at onset	≈10 y	≈1 y
Self-limiting?	In ≈80% of cases by third decade of life	In ≈80% of cases by second decade of life
Counseling?	Intervals/years	Intervals/years
Medication	Continuously/intervals	Continuously/intervals
Social impact	Yes	Yes
Psychological impact	Yes	Yes
Post-disease sequelae		
physical scarring	Yes	Yes
psychological	Yes	Yes

understand that the psychological impact of acne is not strongly correlated with the severity of the disease.^[6]

2.6 Effect of Maintenance Therapy in Acne

For the welfare of patients, and from a public health standpoint, it is important to understand that maintenance therapy for acne can control disease, and, it is hoped, minimize the sequelae of the disorder. Skin biopsy studies have shown that microcomedones, the precursors of all acne lesions, are present even in normal-appearing areas of skin.^[42,43] Furthermore, 28% of sections of normal-appearing skin from patients with acne include histologic features of microcomedones. In addition, biopsy of papules demonstrates the presence of a microcomedo in more than half (52%) of all cases; in comparison, closed and open comedones are detected in 10% and 22% of cases, respectively.^[44]

Although treatment with topical retinoids has been shown to decrease microcomedo concentrations in the skin, microcomedones rebound soon after cessation of therapy.^[43] This may not be readily apparent clinically, since there is a lag time before the appearance of clinical lesions (as would be expected from the time needed for development of acne lesions). Thus, acne experts have theorized that optimal long-term results in acne may be obtained by preventing the development of new microcomedones using an anti-comedogenic agent that targets the microcomedo, such as a topical retinoid.^[7] Clinically, maintenance therapy with topical retinoids has been shown to effectively control acne.^[8-11] However, there are few definitions of maintenance therapy for acne. Studies that have been published to date included a 12- to 16-week maintenance phase, but in the clinical setting, maintenance therapy may last much longer. Furthermore, in one study of maintenance therapy in acne, the investigators found that there was no significant divergence in results between the topical retinoid adapalene and its vehicle until week 12.^[8] They postulated that this was likely due to the lingering efficacy of treatment given during a previous 12-week "treatment phase." Leyden et al.^[9] reported that topical tazarotene monotherapy was comparable to minocycline and combined tazarotene plus minocycline in maintaining acne response at 12 weeks. These results suggest that a longer maintenance phase is needed to more adequately determine the efficacy of any maintenance regimen for controlling acne.

As more studies are conducted, it may be useful to consider examples from other chronic diseases. Often, the success of maintenance therapy is judged by both the time to recurrence and the severity of disease at recurrence. This raises questions about how to best design clinical trials of maintenance therapy in acne. Topical retinoids, either alone or augmented with an antimicrobial, seem a logical choice for maintenance therapy since they target the microcomedo.^[8-11] The therapeutic goal of a maintenance regimen in acne is to prevent new lesions from occurring. There is suffi-

cient evidence showing that subclinical inflammation and hyperproliferation of keratinocytes occur early in comedogenesis. Because retinoids have anti-inflammatory properties and can normalize the process of keratinization,^[7] they seem to be an excellent option for maintenance therapy. Thus, it is recommended that further clinical studies of maintenance therapy in acne include topical retinoids, alone or in combination.

3. Conclusions

There is no doubt among dermatologists that acne is a chronic disease and a very important disease. Furthermore, on the basis of the literature already mentioned, in particular, the epidemiology of acne, the clinical course of acne, and the pharmacoeconomic and psychosocial impact of acne, there is clear evidence that acne is a chronic disease. Furthermore, it is generally accepted that most cases of acne (around 70%) during teenage years are mild, so-called physiologic acne. This type should not be considered a chronic disease but the 30–40% of patients with clinical acne who need continuous consultation and topical and systemic drug support can be considered as having a chronic disease. There is no doubt that those with persisting acne not regressing around age 20 years also belong to this group and the most severe cases, which do not stop at the normal age of around 20 years such as conglobate acne, adrenogenital acne, androgenic acne, and acne inversa are inborn chronic diseases. However, it is absolutely vital for dermatologists and other clinicians interested in acne management to help other healthcare professionals understand the ramifications of this disease. Furthermore, it is essential for patients to know that acne can be a serious, long-lasting disease that often requires long-term and/or maintenance therapy with topical retinoids to prevent relapse. Most importantly, all involved with acne need to be aware that there are now highly effective treatments, for both the acute phase and for maintenance or prevention. Patients with acne have the right to receive the most appropriate treatment by a physician up to date with the medical literature and experienced in the many pitfalls and challenges of acne.

Finally, from a public health standpoint, it is essential for insurers and government regulatory bodies to be aware of the impact of acne. Because the emotional and physical consequences of acne can be severe and life-long, insurers need to reimburse for treatments that have been proven effective against acne. As more treatments for acne become available and widely used, particularly light-based devices, it would behoove insurers to collect data about treatment practices and outcomes, as is done for other chronic diseases. This would provide clinicians with both a scientific and an economic rationale for management decisions. In all likelihood, this type of data may also help patients understand the nature of their disease, adhere to therapy and, in turn, achieve optimal outcomes.

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