

## Infantile Acne Treated with Oral Isotretinoin

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**Abstract:** In contrast to adolescent acne, infantile acne (IA) is a rare condition with only a limited body of available literature. In this descriptive, retrospective study, we reviewed six cases from 2002 to 2010 treated with oral isotretinoin. The average age of onset was 6.16 months (range 0–21 mos). Consistent with the previous, limited literature, we found predominantly boys are affected, a predilection for the cheeks, and a polymorphic inflammatory morphology. Two patients had a family history of acne. All cases were successfully and safely treated with oral isotretinoin. The suggested treatment of childhood acne is similar to that of adolescents (graded according to the severity of the skin disease and risk of scarring). Oral isotretinoin appears to be an effective and safe treatment for severe IA.

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Infantile acne (IA) is a rare disease, and randomized controlled trials are not available to guide treatment. Evidence-based treatment is inferred from studies in older patients but raise relevant safety concerns in children. Oral isotretinoin has been used in children and appears to be an effective treatment for IA. Unbiased reporting of open case series form the realistic best level of evidence for rare diseases in the foreseeable future.

Acne vulgaris is an inflammatory skin disease that affects the pilosebaceous follicle. Adolescent acne is common, with prevalence rates approaching 100% in some populations (1). The pathogenesis involves increased and altered sebum production, follicular hyperkeratinization, *Propionibacterium acnes* colonization, and inflammation. Androgens and a range of other hormones, genetics, and diet have also been suggested as possible etiologic factors (2).

In contrast, childhood acne is uncommon. It is suggested that childhood acne can be classified as neonatal, infantile, mid-childhood, or prepubertal (3). Neonatal acne (3) may appear at birth or during the first 4 weeks of life and may be seen as a physiologic phenomenon. Neonatal acne closely resembles but must not be confused with the common neonatal cephalic pustulosis (3).

In contrast, IA is a rare, inflammatory dermatosis that usually starts at the age of 1 to 16 months and may lead to scarring. It persists throughout infancy and occurs mainly on the cheeks, and its morphology includes all typical elements of acne, including comedo, papules, pustules, and even cysts. The lesions may result in scarring, leaving some degree of disfigurement that requires treatment at a later stage (4). It has been shown that patients with IA are more prone to develop acne vulgaris in adolescence (5).

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A limited number of cases and short series about IA have been published (6–16). Treatment in IA is empirically based on observations in adolescents and adults. It is unlikely that large randomized controlled trials on the treatment of IA will be conducted in the foreseeable future. Additional reporting on the clinical presentation and the effects of therapy therefore appears warranted to provide necessary data for future treatments.

### PATIENTS AND METHODS

Clinical data were collected from the medical and photographic records of all patients with the diagnosis of IA treated with oral isotretinoin from 2000 to 2011 at the Department of Dermatology, Roskilde Hospital, Copenhagen, Denmark, and the Department of Pediatric Dermatology, Hospital del Niño Jesus, Madrid, Spain. The results include the salient aspects of two previously reported cases from Roskilde Hospital and Hospital del Niño Jesus to provide relevant data (6,16). Information was collected on sex, age at onset of acne, morphology, location, severity, family history of acne, and laboratory investigations for hyperandrogenism (androgen, testosterone, hydroxyprogesterone, cortisol, follicle-stimulating hormone [FSH], luteinizing hormone [LH], and sex hormone binding globulin). The duration, effectiveness, and side effects of treatments administered were also recorded.

### RESULTS

We studied six patients, all male. The age of onset of acne was between 0 and 21 months (mean 6.16 mos). In one patient, acne was reported to be present at birth but persisted into early childhood. In the other five patients, ages at onset were 1, 4, 5, 6, and 21 months. The morphology was predominantly inflammatory, showing papules, pustules, and cysts. A polymorphic eruption, with different typical acne lesions within the same patient, was mainly seen. The cheeks were the most involved area (six patients) followed by the chin (two patients). All infants were described as having severe acne. Three had a family history of acne to some degree, but only two had a first-degree relative (mother) with clinically significant acne. None of the patients had other signs of androgenization or systemic disease.

Treatment initially consisted of a variety of topical and oral drugs. No case responded to topical treatments or oral erythromycin, and they were all then treated successfully with oral isotretinoin,



**Figure 1.** Patient 1: infantile acne with inflammatory papules, nodules, and cysts, predominantly on the cheeks.

0.5 mg/kg/day for 4 to 12 months. A summary of the cases is reported in Table 1.

#### Patient 1

A healthy boy presented with an acneiform eruption at birth after an uncomplicated pregnancy and delivery (Fig. 1). The acneiform eruption persisted despite topical treatment with benzoyl peroxide, clindamycin, benzoyl peroxide with clindamycin, and oral erythromycin (200 mg twice daily). At the age of 15 months, the morphology was described as severe papulo-nodulo-cystic acne with scarring, and the child was started on oral isotretinoin at a dose of 0.5 mg/kg/day. Before treatment the child underwent endocrinologic investigations (serum androgens, testosterone, sex hormone binding globulin, FSH, LH, 17-hydroxyprogesterone, and cortisol levels), which were all normal. Hemoglobin, liver enzymes, and lipids were found to be normal before treatment and at follow-up 1 month later. Isotretinoin was administered by emptying the capsule in yogurt for the child to consume. The child experienced diarrhea for 3 weeks and transient perioral exanthema as possible side effects but had no major side effects. His acne improved gradually, and after 12 months of treatment, the skin was clear, and isotretinoin was discontinued after a total cumulative dose of approximately 180 mg/kg (Fig. 2). After follow-up of 2 years, the patient has had no recurrence but is left with scars.

**TABLE 1.** *Characteristics of the Children Studied*

Patient	Sex	Onset age of acne	Morphology of acne	Location of acne	Etiology*	Family history of acne	Treatment
1	Male	0 yrs	Papules, nodules, cystic, scarring	Cheeks bilateral	Normal	Uncle	B, CB, C, and E with no effect I for 12 mos with good effect Side effects: Diarrhea, perioral exanthema See patient 1
2 (Holm and Jemec) (16)	Male	4 mos	Comedones, papules, pustules, nodules, cystic	Cheeks bilateral	Normal	No	A and TI with moderate effect E with moderate effect I for 4 mos with good effect See patient 2
3 (Torello et al) (6)	Male	5 mos	Comedones, papules, nodules, pustules, cysts	Cheeks bilateral	Normal	Mother	TE and E with no effect I for 6 mos with good effect See patient 3
4	Male	21 mos	Deep cysts	Cheeks bilateral	Normal	No	B, C, and F with no effect E with no effect I for 6.5 mos with good effect See patient 4
5	Male	1 mos	Pustules, cysts	Cheeks bilateral, chin	Normal	Mother	C, B, and E with no effect I for 10 mos with good effect See patient 5
6	Male	6 mos	Comedones, papules, pustules	Cheeks bilateral and chin	Normal	No	C and B with no effect I for 12 mos with good effect

\*Objective findings and tests indicating endocrinopathology (serum androgens, serum cortisol, and other hormones).

CB, topical clindamycin/benzoyl peroxide; B, topical benzoyl peroxide; C, topical clindamycin; R, topical retinoid; A, topical azelaic acid; BR, topical benzoyl peroxide/retinoid; E, oral erythromycin; I, oral isotretinoin (retinoid); TI, topical isotretinoin gel; F, topical fucidic acid; TE, topical erythromycin.

### Patient 2

As Holm and Jemec (16) previously reported, a developmentally delayed boy with no family history of acne presented with acne on the cheeks bilaterally at the age of 4 months. Topical treatment with azelaic acid and isotretinoin gel and oral erythromycin was only moderately successful. At the age of 8 months, his acne worsened and evolved into severe cystic acne. He was then treated with oral isotretinoin 0.5 mg/kg/day, which cleared the acne after 4 months, with a cumulative dose of approximately 60 mg/kg. It is unknown whether any recurrence has occurred.

### Patient 3

A case previously reported by Torrelo et al (6) describes a boy, whose mother had severe acne during adolescence, who developed IA at the age of 5 months. The morphology was polymorphic and involved severe cysts. He was treated with topical erythromycin and later 1 month of oral erythromycin without improvement. He was subsequently treated with oral isotretinoin, 1 mg/kg every other day and progressively increased to 1 mg/kg/day. After 6 months of treatment, his lesions had healed, leaving scars. Endocrinology and other laboratory tests were

normal. He had slight lip dryness, but no major side effects. He has had no recurrence during childhood, but at a recent follow-up visit, at the age of 9 years, he had developed incipient comedones, papules, and some pustules on his front, cheeks, and chin.

### Patient 4

A boy with no family history of acne developed acne lesions on the cheeks at the age of 21 months. He was treated unsuccessfully with topical benzoyl peroxide, clindamycin, and fusidic acid and with oral erythromycin (5 mL twice a day at a concentration of 125 mg/5 mL) for 1 month. The lesions worsened, and oral isotretinoin was started at the dose of 1 mg/kg every other day. After 1 month of treatment, the boy had not developed any new lesions and the existing ones had improved. After 5 months of treatment the lesions worsened, and the dose was increased to 1 mg/kg for two consecutive days and a third day of treatment. After 6.5 months of treatment and a cumulative dose of 1100 mg (110 mg/kg), isotretinoin was withdrawn, leaving scars and occasionally active lesions that were easily managed with topical treatment. An endocrinologist examined the boy before treatment was started and laboratory tests were all normal. The treatment was well tolerated and the only side effect was skin chapping in the summer

that resolved with emollients and the occasional use of topical steroids.

#### Patient 5

A boy developed pustules and cysts on the cheeks and chin at the age of 1 month. Treatment with topical clindamycin, benzoyl peroxide, and erythromycin was unsuccessful. Oral isotretinoin was started at the age of 6 months at a dose of 10 mg every other day (0.625 mg/kg/day) and progressively increased to 10 mg for two consecutive days and the third day without treatment. After 4 months of treatment, only postinflammatory hyperpigmented macules without scarring were present. The boy continued treatment for a total of 10 months with a cumulative dose of 1300 mg (162.5 mg/kg). No side effects were reported. The boy was referred to an endocrinologist to exclude hormonal etiology.

#### Patient 6

A 30-month-old boy with no family history of acne presented to our department with a history of comedones, papules, and pustules on the cheeks and chin since the age of 6 months. The lesions had been treated with clindamycin and benzoyl peroxide for a long time with no results. After a complete physical examination and blood and endocrinology tests, oral isotretinoin was started at the dose of 1 mg/kg every other day. The IA cleared after 12 months of treatment with no side effects and with a cumulative dose of approximately 130 mg/kg. At the last visit he had only a few comedones on both cheeks and a few residual scars.

### DISCUSSION

This retrospective study supports previous data concerning the clinical presentation of IA as a disease predominantly affecting boys, with a polymorphic morphology consisting of inflammatory lesions with or without comedones, usually favoring the cheeks (3,7). Scarring occurs as a prominent sequelae and has previously been reported in 17% of patients with IA. Early and effective treatment is needed to prevent disfiguring facial scars (8). The previously reported duration of treatment of IA varies from 6 to 40 months (8).

Information about the treatment of IA is limited. No specific randomized trials have been conducted of IA treatment, and only small case series describe therapy efficacy. The treatment is generally analogous

to the treatment of adolescent acne, using topical or systemic therapies or both according to disease severity (3). Topical treatments including benzoyl peroxide, retinoids, azelaic acid, and antibiotics for noninflammatory acne and oral antibiotics for more significant inflammatory acne are the commonly preferred agents. There are several limitations in the treatment options for IA. Age restricts the use of oral tetracyclines because of the risk of tooth discoloration and bone damage in children younger than 10 years. The oral antibiotic recommended for moderate to severe childhood acne is therefore erythromycin, although problems may occur because of changing resistance patterns in *P. acnes* (3). Oral trimethoprim may be used in cases of erythromycin resistance (8). For obvious reasons, antiandrogen hormonal therapy is not to be used in children, especially boys.

Oral isotretinoin is registered for the treatment of severe acne in adolescents and is the most effective acne treatment currently available. The U.S. Food and Drug Administration has not approved the use of oral isotretinoin in children younger than 12 years, and it therefore can be used only as an off-label treatment, so the use of oral isotretinoin has been reported in only a small number of IA cases (6–16) (Table 2). The five severe IA cases presented here were treated with isotretinoin according to the same guidelines as its use in adolescents and older children. Severe childhood acne has been successfully and



**Figure 2.** Patient 1: infantile acne after treatment with oral isotretinoin for 12 months.

**TABLE 2.** Summary of Patients with Infantile Acne Treated with Oral Isotretinoin

Reference	Sex	Onset age of acne, months	Isotretinoin dosage, mg/kg/day	Duration, months	Side effects
Burket and Storrs (12)	Female	18	0.5–1	5	Reduced hair growth, mood changes, high lactate dehydrogenase
Arbegast et al (9)	Male	2 (comedones) 10 (cystic)	0.36–0.67	5	High serum glutamic-pyruvic transaminase and glutamic-oxaloacetic transaminase
Horne and Carmichael (13)	Male	12	1	4	Mild eczema on neck
Leaute-Labraze et al (14)	Male	6	0.5	4	None
Mengesha and Hansen (15)	Female	20	1 then 2 (+ prednisolone)	6 5	Transient umbilical granulation
Cunliffe et al (8)	Male	?	0.5	4	?
Sarazin et al (10)	Female	20	0.5–0.6	7	None
Barnes et al (11)	Female	6	0.2–1.5	14	None
	Female	7	0.5	5	None
Hello et al (7)	Male	9	?		None
	Male	6	?		None
Miller et al (this article; patient 1)	Male	0	0.5	12	Transient perioral exanthema, diarrhea 3 wks
Holm and Jemec (16)	Male	4	0.5	4	None
Torello et al (6)	Male	5	0.5–1	6	Slight lip desquamation

?, unknown.

safely treated with oral isotretinoin in at least 11 other cases in addition to our two case reports (6–16). The dose regime is typically 0.5 mg/kg/day, and a cumulative dose lower than 120 mg/kg has been associated with relapse (11), but there have been reports that lower dosages in teenagers is associated with low rates of recurrence (17). The ideal cumulative dose is not known, but our cases received from 60 to 162.5 mg/kg before the acne cleared.

Monitoring patients for the well-described adverse effects of isotretinoin is mandatory (18). Isotretinoin has been used for very young children with neuroblastoma in a randomized controlled trial; adverse effects were identical to those seen in adults (19), including dryness of the skin and mucosae, sun sensitivity, and biochemical abnormalities such as anemia and high liver enzymes and lipids. Although depression and suicidal ideation may rarely occur in teenagers, this is not recordable in infants. There have also been some reports of bone toxicity (calcification of tendons and ligaments and premature epiphyseal closure) (20). None of the six cases treated with oral isotretinoin in this study experienced any major side effects.

Drug intake can be a challenge in infants. Isotretinoin is marketed as capsules, which may be difficult for infants to swallow, and there is a risk of upper airway obstruction. Furthermore, dosages usually do not correlate with the dose in the capsules. In addition, light and oxygen degrade isotretinoin, so the powder within the capsules cannot be exposed to daylight. After opening the capsules in a dark or dim room, isotretinoin powder can be added to yoghurt,

as mentioned in one of our cases. Alternatively, capsules may be frozen and added to a candy bar (11).

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