Difficult-to-treat acne and acne imitator

January 20, 2022

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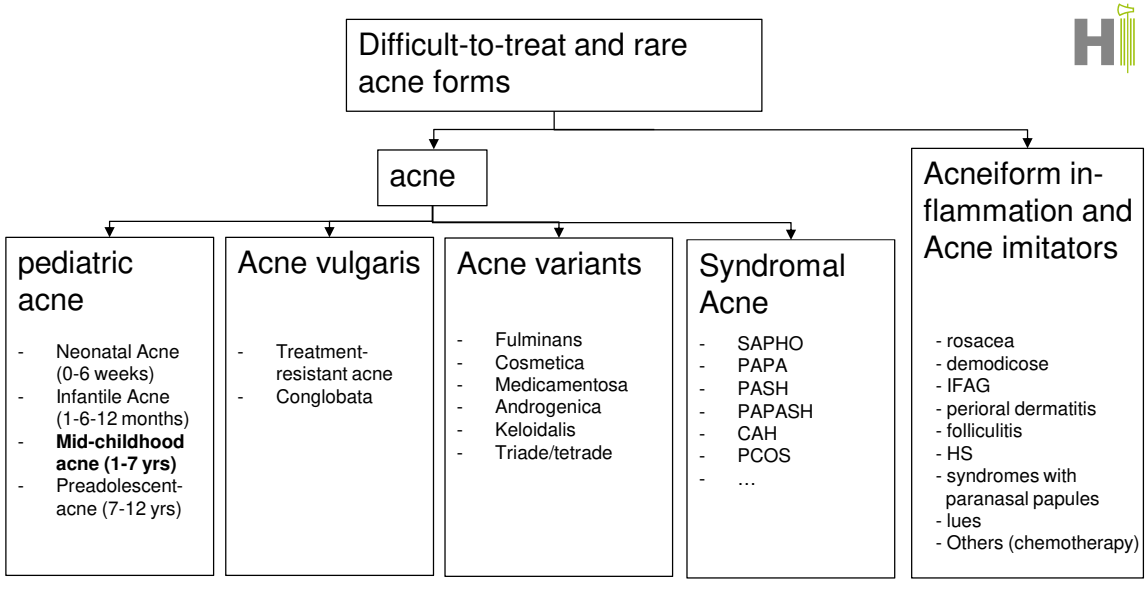
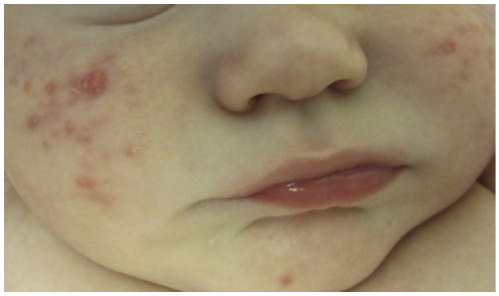


Neonatal acne, 0-4 weeks

Pathogenesis:
- Physiologic abrupt decrease of maternal estrogen after birth
- hypophyseal release of gonadotropins (LH/FSH)
- transient DHEAS production
- androgenic acne eruptions

DD:
- neonatal cephalic pustulosis
- early onset CAH
- Maternal corticosteroid/lithium, diphenylhydantoin intake (antiepileptic)



Cave! Congenital adrenal hyperplasia
- Additional virilization signs, e.g. growth parameters, blood pressure, precocious sexual maturation
- Undervirilization/hypogonadism
- Vomiting due to salt wasting, dehydration, death

Endocrinology (DHEAS, free testosterone, ..)

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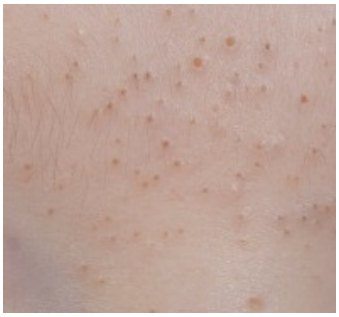
Neonatal acne or cephalic pustulosis?

Tab. 1 Aknetherapeutika und ihre Wirkung auf den Komedo

Wirkstoffe	Komedolytisch	Antikomedogen
Tretinoin	++	++
Isotretinoin (t/s)	++	++
Adapalene	++	++
Tazarotene	++	++
Trifarotene	++	++
Azelainsäure	(+)	+
Salicylsäure	+	(+)
Benzoylperoxid	+	?
Clindamycin	?	+

++ stark, + moderat, (+) schwach
t topisch, *s* systemisch



Neonatal cephalic pustulosis
- frequent, but no comedones
- Malassezia colonization
- Topical ketoconazole

True comedonic acne, mainly on forehead, cheecks, nose
- topical retinoids
- topical azelaic acid
- topical benzoyl peroxide
- rarely macrolide antibiotics in severe acne eruptions or in case of scarring

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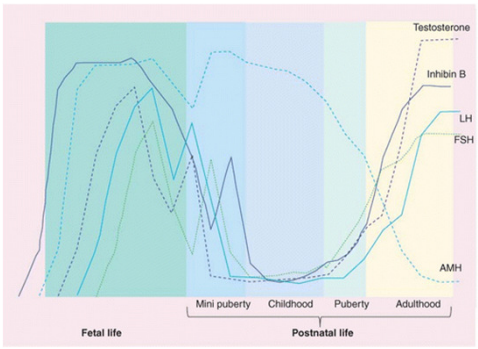
Karoglan et al., Hautarzt 2021;72:815

Infantile acne (1-12 months) ≠ (acne infantum!)

Most cases of infantile acne are **not** associated with endocrinological disorders!



Male hypogonadism,
Pediatric Health Vol 4, No.5, 2020

Gonadal production of testosterone:
Perinatal decrease of maternal hormones
Hypophyseal increase of LH/FSH
Stimulation of gonadal testosterone production in boys, not in girls
Mini puberty during first year of life

No gonadal androgen production in girls, rapid decrease of testosterone within the first 2 weeks of life

Adrenal androgen production:
Continuous decrease of adrenal androgen production during 1st year via involution of Zona reticularis of adrenal glands (DHEA/S production)

Genetic predisposition:
More severe infantile acne in families with severe parental acne history

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Course of disease and diagnostics
- Severe infantile acne is more frequent in families with **history of severe acne**
- Predictive for more severe adolescent acne vulgaris
- Most patient do not require extensive evaluation of androgen-/corticosteroid-secreting disorders
- Pubic hair, testicular enlargement, recalcitrant or severe and rapidly developping acne may require further evaluation
  - Bone age assessment
  - LH, FSH, free testosterone, DHEA(S) measurement/referral to pediatric endocrinologist

Treatment
- essentially like acne in any age
- BP, topical retinoids or fixed combination therapies
- **oral erythromycin** in inflamed lesions
- Rarely: Propionibacterium acnes resistance to erythromycin **TMP-SMX**
- Recalcitrant, scarring acne: **oral isotretinoin**
  - **Oral suspension (Insel pharmacy, 10mg/ml)**
  - Freezing and cutting capsules, feed via hiding in candy bar (!)
  - Feed isotretinoin after opening capsules and dissolve it in a spoon full of luke warm milk

boy, 8 months, with comedones, inflammatory papules, pustules with infantile acne

Dermatol Clin 2016;34:195-202

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DD infantile acne

- **Acne venenata infantum** or pomade acne
- corticosteroid-induced acne is seen in the perioral, periocular, and infranasal areas due to topical, oral, and inhaler corticosteroids
- chloracne is seen in the centrofacial region due to accidental exposure to chlorinated aromatic hydrocarbons.
- **perioral dermatitis, milia, and miliaria**

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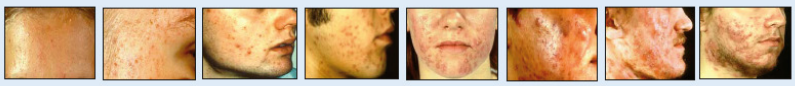
Akne Therapie Schema

Empfehlungen der Global Alliance to improve Outcomes in Acne adaptiert durch das Advisory Board: Prof. Monica Harms, Genève; Dr. Martin K. Kägi, Zürich und Dr. Pier-Paolo Pedrazzetti, Adliswil



	Leicht		Mittelschwer	Schwer	
	Komedonale Akne	Papulopustulöse Akne	Papulopustulöse Akne	Noduläre Akne[2]	Noduläre Akne A. conglobata
1. Wahl[1]	Topisches Retinoid	Top Retinoid + BPO +/- top. Antibiotikum	Orales Antibiotikum + top Retinoid +/- BPO	Orales Isotretinoid	Orales Isotretinoid[3]
Alternativen[1]	Anderes topisches Retinoid oder BPO oder Desinfizientia (z.B. Chlorhexidin oder Salizylsäure)	Anderes top Rentinoid + anderes top antibakterieles Arzneimittel oder Azelainsäure*	+ Anderes orales Antibiotikum + anderes top Retinoid +/- BPO	Orales Antibiotikum + top Retinoid +/- BPO	Orales Antibiotikum + top Retinoid + BPO
Alternativen für Frauen[1,4]	Siehe 1. Wahl Lipoxyhydroxy-Säure[1]	Siehe 1. Wahl top Erythromyzin[4]	Orales Antiandrogen[5] +/- top antibakterielles Arzneimittel	Orales Antiandrogen[5] +/- Orales Erythromyzin +/- anderes top antibakterielles Arzneimittel	Hohe Dosis orales Antiandrogen[5] +/- anderes top antibakterielles Arzneimittel
Erhaltungstherapie	Topisches Retinoid +/- BPO				

1 – Eventuell mechanische Entfernung von Komedonen; 2 – Mit kleinen Knoten (>0,5–1cm); 3 – zweiter Behandlungsdurchgang bei Rezidiv;
4 – Bei möglicher Schwangerschaft, siehe Publikation Gollnik H et al. (2003 J Am Acad Dermatol 49(1): S1–37;
5– Siehe Publikation Gollnik H et al. (2003 J Am Acad Dermatol 49(1): S1–37;
* Bezüglich dieser alternativen Empfehlung wurde kein Konsens erzielt, aber in einigen Ländern ist das Verschreiben von Azelainsäure übliche Praxis

Dr. M. Theiler

UNIVERSITÄTS-KINDERSPITAL ZÜRICH

acne – topical treatment

Topical retinoids
- Comedolytic
- Anticomedogenic
- Initiation and maintenance treatment
- Irritant (increase freq. gradually)

BPO
- Desinfectant
- antiinflammatory
- Irritant
- Bleaching
- (possible in pregnancy)

Azelaic acid
- Anticomedogenic
- Only slightly comedolytic
- Maintenance therapy
- (possible in pregnancy)

Fixed combination preparation

Name	drugs
Epiduo/Forte	Adapalen, Benzoylperoxid
Acnatac	Tretinoin, clindamycine
Duac	BP, clindamycine
Acne Creme plus Widmer	BP, miconazol nitrate

acne – systemic treatment

Systemic antibiotics
- antiinflammatory
- > 8 yrs low-dose tetracycline
- < 8 yrs oral erythromycine (40mg/kg/d, 6-12 weeks) or TMP-SMX (in case of P. acnes resistance to erythromycin)
- Always combine with topical treatment (BP)

systemic Isotretinoin
- All severe acne, all ages!
- Sebostatic, comedolytic, antiinflammatory, antibacterial
- **Shortens course of disease in acne**
- Oral suspension available at the Inselspital Bern (10mg/ml)
- dosing 0.3 – 1mg/kg/d

systemic dapsone fatol
- Severe acne
- Together with isotretinoin or instead of isotretinoin in II-AF (iso-induced acne fulminans)
- antiinflammatory, antibacterial
- Not licensed in CH

oral contraception in adolescent patients
Or
Isolated antiandrogenic treatment
(spironolacton, cyproteronacetate)

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Midchildood acne (1-7 yrs): rarest form of acne

Appearance of **true acne in this age group** should raise concern for underlying causes of hyperandrogenemia,

Cushing Syndrome, late-onset congenital adrenal hyperplasia, adrenal or gonadal androgen-secreting tumors

- History
- Clinical examination
- Lab
- Ultrasound abdomen (follicle count)
- Treatment of acne (in conjunction with endocrinological therapy)

Dermatol Clin 34 (2016):195-202 and references therein

Eichenfield et al, pediatrics 2013

Basak et al, pediatr rev. 2013

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mid-childhood acne in a 4 yrs old girl

Mother remarked **increased body-odor (perspirational smell)** in axilla, no further clinical hyperandrogen symptoms

Pathologic hormone status, non-classic adrenogenital syndrome AGS

Nebennieren- und Gonadenfunktion - Blut	
Luteinisierendes Hormon (LH) [< 2.14] [U/L]	0.6
Follikelstim. Hormon (FSH) [0.62 - 6.37] [U/L]	1.0
Beurteilung der Gonadotropine	.
Testosteron basal [0.1 - 0.4] [nmol/L]	0.2
Androstendion basal [0.4 - 0.6] [nmol/L]	0.8
Dehydroepiandrosteron-S basal [< 0.1] [µmol/L]	2.8
17-OH-Progesteron basal [0.4 - 1.5] [nmol/L]	0.6

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Picture, case: Dr. M. Theiler, Zürich

mid-childhood acne in a 2 year old boy age suspicious for syndromal acne!

Known Li-Fraumeni-Syndrom
(p53 functional deficit)

Increased risk of **adrenocortical carcinoma** (among others) with androgen secretion

For dermatologists: melanoma and BCC incidence also increased

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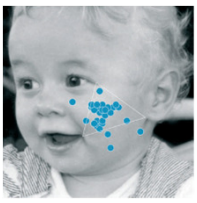
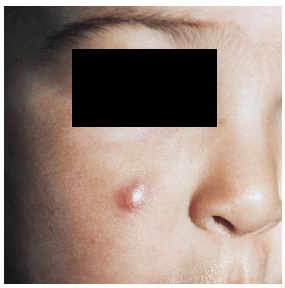
Picture, case: Dr. M. Theiler, Zürich

IFAG, idiopathic facial aseptic granuloma





- Abscess-like nodule, pot. fluctuating
- Rarely multiple
- Sterile
- **Association with chalazion and later rosacea**
- Frequently with eye involvement
- Exclude leishmaniosis (history, ev. biopsy)

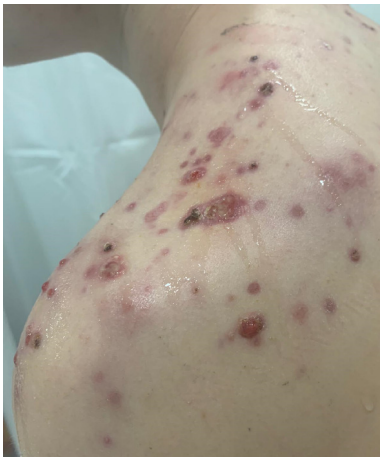
Dermatology Online Journal 2010;16 (1): 9, Roul S. Arch Dermatol 2001, Boralevi F. Br J Dermatol 2007 Pediatric Dermatol 2013;30:429

Preadolescent acne (7-12 yrs)

- Comedonic acne in T zone frequently the first sign of (pre)puberty
- No further investigations in absence of other signs of androgen excess
- Physiologic awakening of adrenal gland activity (6-7 in girls, 7-8 in boys, DHEAS increase)
- **Current trend toward a decreasing age of puberty onset in the Western world explains the increasing incidence of «preadolescent» acne**
- Treatment analogous to acne vulgaris treatment **(use simple treatment regimens!)**

Dermatol Clin 2016;34:195-202

Acne fulminans
AF-SS and AF-WOSS



- 13 yr old boy
- Isotretinoin 10mg/day for facial acne for 30 days

- Ulcerated nodules
- No pain, no fever
- No joint ache
- No pp pustulosis
- CRP 4mg/l, ESR 30mm/h

Diagnose?

Acne fulminans AF-SS/AF-WOSS

- Rare event, only about 200 published cases
- Male predominance 10:1, Caucasian race predominance
- Isotretinoin-induced (II): IIAS-SS or IIAS-WOSS
- DD: SAPHO (on average older, with female preponderance)
- DD: PASH, PAPA, PAPASH
- Lab: blood count, liver function test, CRP, ESR, imaging if bone/joint involvement

STOP Isotretinoin

↓

START Corticosteroid 0.5-1mg/kg at least 4 weeks in AF-SS/2 weeks AF-WOSS, until healing of crusted lesions

↓

(If flaring persist, **add Dapsone 50-100mg/day**, then CsA, then TNFα antibodies)

↓

RESTART Isotretinoin not earlier than after first healing started (low dose 0.1mg/kg) with steroid overlap over at least 4 weeks

Prolonged steroid treatment: consider PPI, bone protection, PCP prophylaxis (but most panelists did not consider ulcer prohylaxis in low risk patients)

Greywal et al, Evidence-based recommendations for the management of acne fulminans and ist variants JAAD 2017;77:109

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Spontaneous acne fulminans

Begin acne 01/21, **no arthritis, no myalgia**
Severe pustular form 03/21
04/21 Start Isotretinoin 20mg/Spiricort 50mg
06/21 Stop Iso/ continue Spiricort 50/doxy 200mg

Zurich childrens hospital:
07/21 stop doxycycline, start dapsone 100mg
continue Spiricort 50mg

continuous reduction of cortison, stop 08/21

start Isotretinoin 20mg/d with cont'd dapsone

pictures/case: Dr. L. Weibel, Kinderspital Zürich

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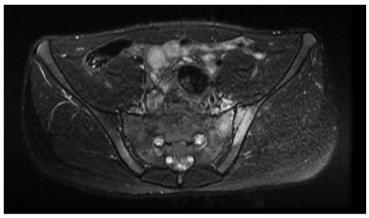
Isotretinoin side effects for bone/joint

- (exercise-associated) myalgia and dysarthria, CK increase
  reduce exercise or reduce isotretinoin dose
- Vertebral hyperostosis (DISH-like disease)
- Calcification of ligaments
- Premature epiphyseal fusion
- sacroileitis/spondarthropathies
  - In larger cohort studies up to 10%, specifically in Turkey/near east regions
  - Symptomatic approx 2-3 months after start of isotretinoin, ev. with worsening of acne
  - Stop isotretinoin, establish NSAR, ev. CS, MTX or TNFα antibody
  - Bone/joint normalization within 6-12 months

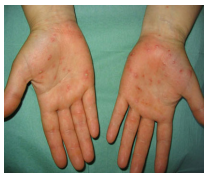


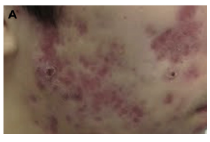
Elnady B et al, Clin Rheumatol 2020
Alkan S et al, J Rheumatol 2015
Karaosmanoğlu N et al, BMC Musculoskeletal disorders 2020
Baykal L et al, Cutan Ocul Toxicol 2017

SAPHO – synovitis, acne, pustulosis, hyperostosis, osteitis

- Young adults, female preponderance
- Isotretinoin as a treatment for acne may trigger stronger inflammation in SAPHO (neutrophilic burst)

- Treatment options:
  - Systemic steroids, MTX
  - TNFα blocker
  - IL1 blocker
  - apremilast





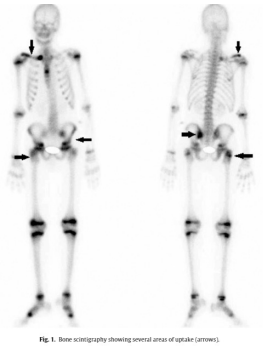
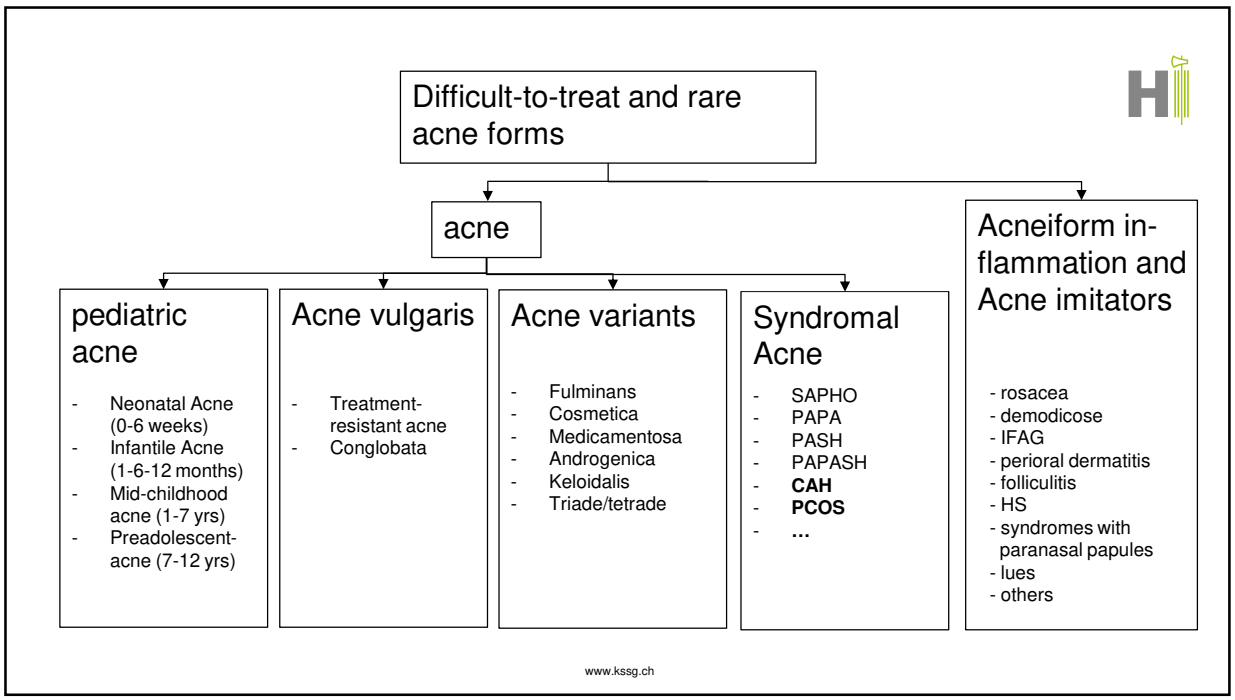


Fig. 1. Bone scintigraphy showing several areas of uptake (arrows).

Kolios et al., Br J Dermatol. 2018 Oct;179(4):959-962



When to suspect hormonal factors for acne, and how to plan the blood test

- Early, severe acne
- Menstrual history of amenorrhea, oligomenorrhea
- Hirsutism (70% of hirsute female suffer from hyperandrogenism)
- Acanthosis nigricans
- Androgenetic alopecia (SAHA: seborrhoe, acne, hirsutism, alopecia)
- Virilization signs (clitoromegaly, increased libido, deepening of voice, increased muscle mass, decreased breast size, male hair pattern growth, premature body-odor changes)
- Diabetes mellitus (due to insulin resistance)
- Other dermatological disorders (rosacea, seborrheic dermatitis)
- Cushingoid face, habitus

When to draw blood for hormonal disorders:

- **Leave it to your endocrinologist/gynecologist..**
- Early morning fasting blood sample
- Blood test during menstrual period (day 1-3), or fasting in amenorrheic women
- No blood test during ovulation (surges of hormones)
- Discontinue oral contraceptives for 4-6 weeks prior to testing

Basic blood tests:

Testosterone free total, LH, FSH, LH/FSH ratio, DHEAS, Insulin, Prolactin, TSH, SHBG, PSA, Cortisol, blood sugar, lipid profile

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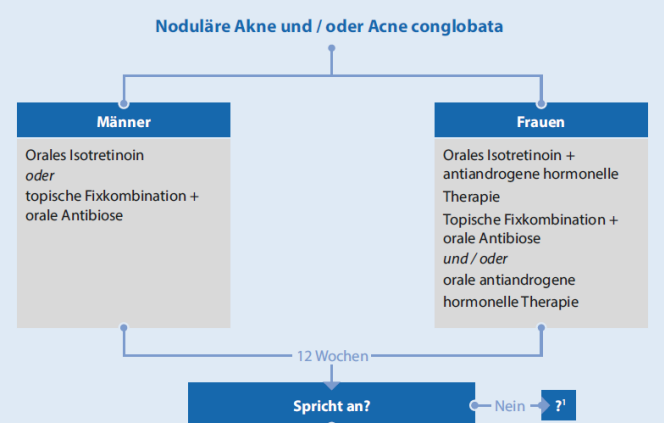
OCP in female with severe acne

- Ethinyl estradiol-containing OCP
- Progestin as combination: (nor)gestrel
- Discuss peripheral androgen inhibitors with gynecologists if therapy-resistance (spironolactone, cyproteronacetate, drospirenon)



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High versus low dose isotretinoin treatment duration follow up tests

Cochrane Library
Cochrane Database of Systematic Reviews

2019

Oral isotretinoin for acne (Review)

Costa CS, Bagatin E, Martimbianco ALC, da Silva EMK, Lúcio MM, Magin P, Riera R

- Clinical trial evidence for oral isotretinoin conducted around 30 years ago was **low quality**, meta-analysis not possible due to heterogeneity of studies and clinical assessments[3]
- **No solid evidence in favor for high or low dose isotretinoin**, but daily treatment may be more effective than treatment for one week each month[3]
- Cumulative dosage 120-150mg/kg vs treatment until clearance of acne plus 1 to 2 months, recommendation of the **Global Alliance to Improve Outcomes in Acne**[1,2,4,5]
- **Neither daily nor cumulative dose had an effect on the relapse rate as long as treatment was continued for at least 2 months after the complete resolution of acne lesions**[2]
- **Follow up measurements**[5]**:** Lipids, ALT/AST, CK, GGT, pregnancy
- Isotretinoin and **depression** …. To be followed up

1 Tan et al., J Cutan Med Surg 2016(20:13-20
2 Rademaker et al., Int J Dermatol 2016;55:518-523
3 Costa et al., Cochrane analysis, 2019
4 Thiboutot et al., JAAD 2018;78:S1-S23
5 Landis et al., Am J of Clin Dermatol 2020;21:411

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Summary

- Mid-childhood acne shows strongest association with hormonal disturbances remain suspicious in 1-7 yrs old children with acne
- Joint ache/strong inflammation: syndromal acne?
  CS as emergency treatment, stop isotretinoin
- Start early with isotretinoin in acne lesions (papulopustular smoldering acne should be treated appropriately)
- No clear evidence for high vs low dose isotretinoin
- CK increase: adapt physical training, dose reduction possible, but not compulsory (CK doubling/tripling w/o symptoms)
- OCP ideally with EE/(nor)gestrel or peripheral antiandrogen combination (spironolacton, cyproteronacetate, drospirenon): consult with your gynecologist!

Ein Dankeschön an
- Lisa Weibel und Martin Theiler, ZH
- Valérie Hauser, SG