Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2019-B-086 Trifaroten

Stand: Juli 2019

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Trifaroten [Akne vulgaris] **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe unter *II. Zugelassene Arzneimittel im Anwendungsgebiet*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	„nicht angezeigt“
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Trifaroten Aklief®	Trifaroten ist angezeigt zur lokalen Therapie der Acne vulgaris im Gesicht und/oder am Rumpf bei Patienten ab zwölf Jahren, wenn viele Komedonen, Papeln und Pusteln vorhanden sind.
Topische Therapien	
Tretinoin ATC: D10AD01 Cordes® VAS Creme	Akne vulgaris.
Adapalen ATC: D10AD03 Differin 0,1% Crème/Gel	Zur äußerlichen Anwendung bei Akne vulgaris im Gesichtsbereich, wenn Komedonen überwiegen und Papeln und Pusteln vorhanden sind.
Bezoylperoxid Benzaknen® 5, 10 Gel, Wash 5% Suspension	5%: Alle Formen der Akne in milder bis mittlerer Ausprägung. Das Arzneimittel wird angewendet bei Jugendlichen (ab 12 Jahren) und Erwachsenen. 10%: Alle Formen der Akne schwerer Ausprägung sowie Akneerkrankungen, bei denen die Anwendung einer niedriger konzentrierten Benzoylperoxid-Zubereitung nicht zum Therapieerfolg führt. Das Arzneimittel wird angewendet bei Jugendlichen (ab 12 Jahren) und Erwachsenen. Das Arzneimittel dient insbesondere der Anwendung an Brust und Rücken und wird bei Patienten eingesetzt, die auf niedrigere Benzoylperoxidkonzentrationen nicht ausreichend ansprechen. Wash 5%: Zur Behandlung aller Formen der Akne in leichter Ausprägung sowie zur unterstützenden Therapie bei Akne mittlerer bis schwerer Ausprägung, ab zwölf Jahren. *Benzoylperoxid ist ein apothekenpflichtiges Arzneimittel, das nicht erstattungsfähig ist, sofern der Patient älter als zwölf Jahre bzw. bei Menschen mit Entwicklungsstörungen älter als 18 Jahre ist (§§ 31 Absatz 1 Satz 1 SGB V i.V.m. 34 Absatz 1 Satz 5 Nr. 1 und 2 SGB V).*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Azelainsäure ATC:D10AX03 Skinoren® 20% Creme	Topische Behandlung der Akne vulgaris.
Erythromycin ATC: D10AF02 Aknemycin Lösung	Alle Formen der Akne, insbesondere entzündliche Formen mit Papeln und Pusteln.
Clindamycin ATC: D10AF01 Zindaclin 1% Gel	Zur Therapie der leichten bis mittelschweren Akne vulgaris.
Nadifloxacin ATC: D10AF05 Nadixa 10 mg/g Creme	Zur äußerlichen Anwendung bei leichten bis mittelschweren Ausprägungen entzündlicher Formen der Akne vulgaris (Akne papulo-pustulosa Grad I-II).
Chlortetracyclin ATC: D06AA02 Aureomycin®	Entzündliche Akne im Gesicht.
Natriumbituminosulfonat ATC: D10AX12 z.B. Aknichthol® soft Emulsion	Zur Verminderung der Komedonenzahl bei leichter und mittelschwerer Akne vulgaris. *Natriumbituminosulfonat ist ein apothekenpflichtiges Arzneimittel, das nicht erstattungsfähig ist, sofern der Patient älter als zwölf Jahre bzw. bei Menschen mit Entwicklungsstörungen älter als 18 Jahre ist (§§ 31 Absatz 1 Satz 1 SGB V i.V.m. 34 Absatz 1 Satz 5 Nr. 1 und 2 SGB V).*
Topische Kombinationstherapien	
Fixkombination Adapalen und Benzoylperoxid ATC: D10AD53 Epiduo® 0,1%/2,5% Gel	Topische Behandlung der Akne vulgaris bei Vorliegen von Komedonen, Papeln und Pusteln. Epiduo ist angezeigt bei Erwachsenen, Jugendlichen und Kindern im Alter von neun Jahren und darüber.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Fixkombination topisches Clindamycin und Tretinoin ATC: D10AD51 Acnatac® 10mg/g + 0,25mg/g Gel	Acnatac wird zur topischen Behandlung von Akne vulgaris angewendet, wenn Komedonen, Papeln und Pusteln bei Patienten ab zwölf Jahren vorhanden sind
Fixkombination Clindamycin und Benzoylperoxid ATC: D10AD53 Duac® 10mg/g + 30mg/g Gel oder Duac® Akne Gel	Das Gel wird angewendet zur topischen Behandlung der leichten bis mittelschweren Akne vulgaris, insbesondere mit entzündlichen Läsionen bei Erwachsenen und Jugendlichen ab zwölf Jahren.
Fixkombination topisches Isotretinoin und Erythromycin ATC: D10AD54 Isotrexin® Gel	Isotrexin ist angezeigt zur topischen Behandlung der mittelschweren Akne. Die offiziellen Richtlinien für den angemessenen Gebrauch von antimikrobiellen Wirkstoffen sind zu berücksichtigen.
Fixkombination topisches Tretinoin und Erythromycin ATC: D10AD51 Aknemycin® Plus	Alle Formen der Akne, sowohl nicht-entzündliche Formen mit Komedonen als auch entzündliche Formen mit Papeln und Pusteln, insbesondere bei seborrhoischer Haut.
Systemische Therapien	
Isotretinoin ATC: D10BA01 Isotretinoin-ratiopharm® 10 mg Weichkapseln	Schwere Formen von Akne (wie noduläre Akne oder Acne conglobata oder Akne mit Gefahr einer dauerhaften Narbenbildung), die gegenüber angemessenen Standardbehandlungszyklen mit systemischen Antibiotika und lokaler Behandlung therapieresistent ist.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Doxycyclin ATC:J01AA02 Doxakne® 50 mg	1. Akne papulo-pustulosa (entzündliche Form der Akne). 2. Therapieversuch bei Akne conglobata. Kinder unter 8 Jahren dürfen Doxycyclin nicht einnehmen. Das Arzneimittel ist zugelassen zur Anwendung bei Erwachsenen und Jugendlichen über 12 Jahren.
Doxycyclin ATC:J01AA02 Doxycyclin Heumann 100 mg	[…] 5. Hauterkrankungen, auch infizierte schwere Formen der Akne vulgaris und Rosacea. Die offiziellen Richtlinien für den angemessenen Gebrauch von antimikrobiellen Wirkstoffen sind bei der Anwendung von Doxycyclin zu berücksichtigen.
Minocyclin ATC: J01AA08 Aknosan Filmtabletten	Schwere Formen der Akne (Acne vulgaris). Offizielle Empfehlungen zum angemessenen Gebrauch von Antibiotika sollten berücksichtigt werden.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2019-B-086 (Trifaroten)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	7. Juni 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

„…kutane Behandlung der Akne vulgaris im Gesicht und / oder am Rumpf bei Patienten ab neun Jahren, wenn viele Komedonen, Papeln und Pusteln vorhanden sind.“

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation: *Akne vulgaris* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 09.05.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 289 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 8 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

keine

3.2 Cochrane Reviews

Costa CS et al., 2018 [2].

Oral isotretinoin for acne

Fragestellung

To assess efficacy and safety of oral isotretinoin for acne vulgaris.

Methodik

Population:

- participants with acne vulgaris who had been clinically diagnosed by a physician

Intervention:

- Oral isotretinoin

Komparator:

- Isotretinoin different dose, placebo or other systemic or topical active therapies; oral isotretinoin plus systemic or topical active therapies

Endpunkte:

- Primary outcomes
  - Improvement in acne severity assessed by a decrease in total inflammatory lesion count, measured in participants who were treated for a minimum period of 16 weeks.
  - Frequency of serious adverse effects
- Secondary outcomes
  - Improvement in acne severity assessed by the following tools:
    - i) Participant's self-assessment of acne severity; and
    - ii) Physician's global evaluation of acne severity
  - Changes in quality of life (QoL) assessed using a validated instrument
  - Frequency of less serious adverse effects
  - Dropout rates

Recherche/Suchzeitraum:

- Cochrane Skin Group Specialised Register, CENTRAL,MEDLINE, Embase, PsycINFO and LILACS were searched up to July 2017; we updated this search in March 2018, but these results have not yet been incorporated in the review.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 31 RCTs, involving 3836 participants

Charakteristika der Population:

- 2 to 55 years
- with mild to severe acne
- twice as many male participants as females (2229 men and 1081 women)
- sample size varied from 16 to 925 participants

Qualität der Studien:

- (siehe Anhang, Abbildung 4)

Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

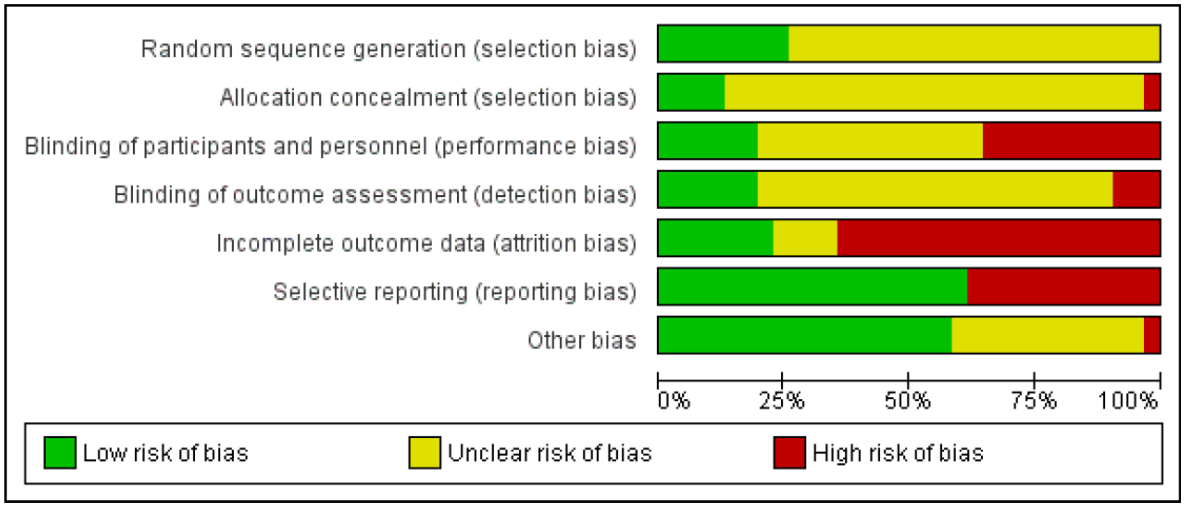


Abbildung 1: Summary Graph Risk of Bias all included studies, Costa et al.

Studienergebnisse:

- 1. Oral isotretinoin versus oral antibiotics plus topical agents: oral isotretinoin versus azelaic acid cream plus minocycline (Gollnick 2001), oral isotretinoin versus tetracycline plus topical adapalene gel (Oprica 2007), and oral isotretinoin versus adapalene/benzoyl peroxide gel plus doxycycline (Tan 2014);
  - o Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (treatment for at least 16 weeks): Overall, oral isotretinoin did not have a greater effect on improving acne severity than any combination of oral antibiotic plus topical agent after 20 to 24 weeks therapy (RR 1.01 95% CI 0.96 to 1.06; participants = 400; studies = 3; I^2 = 46%);
  - o Primary outcome: Frequency of serious adverse effects: The risk of serious adverse effects was three times higher with oral isotretinoin than with oral antibiotics plus topical agents but the confidence interval was very wide and included 1 (RR 3.00, 95% CI 0.12 to 72.98; participants = 400; studies = 3; I^2 = 0%);
  - o Improvement in acne severity assessed by physician's global evaluation: Overall, when oral isotretinoin was compared with any combination of oral antibiotic plus topical agent, themeta-analysis showed a 15% higher improvement in acne severity with oral isotretinoin for this outcome (RR 1.15, 95% CI 1.00 to 1.32; participants = 351; studies = 2; I^2 = 68%);

- 2. Oral isotretinoin versus oral isotretinoin plus topical agents: clindamycin 1% daytime plus adapalene 0.1% at bedtime (Dhir 2008), and 5% dapsone gel (Faghihi 2014);
  - Primary outcome: no available data;
  - Primary outcome: Frequency of serious adverse effects: There were no serious adverse effects in either RCT which had addressed the comparison of oral isotretinoin versus oral isotretinoin plus topical agents;
  - Improvement in acne severity assessed by participant's self-assessment of acne severity: no available data;
- 3. Oral isotretinoin versus 0,1% tretinoin cream plus 5% benzoyl peroxide gel (Leheta 2011);
- 4. Oral isotretinoin versus chemical peeling with trichloroacetic acid (TCA) 25% (Leheta 2011);
- 5. Oral isotretinoin versus oral isotretinoin plus oral antibiotic: azithromycin pulse (De 2011), and erythromycin (Jones 1983b);
  - Primary outcome: no available data;
  - Primary outcome: Frequency of serious adverse effects: There were no serious adverse effects;
  - Improvement in acne severity assessed by participant's self-assessment of acne severity: only results from one study;
- 6. Oral isotretinoin versus azithromycin (Wahab 2008);
- 7. Oral isotretinoin versus erythromycin (Jones 1983b);
- 8. Oral isotretinoin versus minocycline (Pigatto 1986);
- 9. Oral isotretinoin versus tetracycline (Lester 1985);
- 10. Oral isotretinoin versus dapsone (Prendiville 1988);
- 11. Oral isotretinoin versus etretinate (Goldstein 1982);
- 12. Different doses or therapeutic regimens of oral isotretinoin (Agarwal 2011; Ahmad 2015; Akman 2007; Corlin 1984; Cumurcu 2009; Dhaked 2016; Farrell 1980; Jones 1983a; Kapadia 2005; King 1982; Lee 2011; Shetti 2013; Strauss 1984; Van der Meeren 1983);
  - Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (after at least 16 weeks): no meta-analysis possible, caused by heterogenous data;
  - Primary outcome: Frequency of serious adverse effects: There was no report of any serious adverse event in 14 RCTs on different doses/regimens of oral isotretinoin (n= 906). The quality of the evidence was low due to very serious limitations of design in the studies;
  - Improvement in acne severity assessed by participant's self-assessment of acne severity: no available data;
- 13. Standard oral isotretinoin versus other formulations of oral isotretinoin: standard isotretinoin versus micronised isotretinoin (Strauss 2001), and standard isotretinoin versus isotretinoin-Lidose (Webster 2014);
  - Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (after at least 16 weeks): no meta-analysis possible;
  - Primary outcome: Frequency of serious adverse effects: no meta-analysis possible;

- o Improvement in acne severity assessed by participant's self-assessment of acne severity: no meta-analysis possible

- 14. Oral isotretinoin versus placebo (Peck 1982; Rademaker 2013b).
  - o Primary outcome: Improvement in acne severity assessed by a decrease in total inflammatory lesion count (after at least 16 weeks): no available data;
  - o Primary outcome: Frequency of serious adverse effects: No serious adverse effects were detected in participants from both included RCTs which compared oral isotretinoin with placebo;
  - o Improvement in acne severity assessed by participant's self-assessment of acne severity: no meta-analysis possible

Fazit der Autoren

Evidence was low-quality for most assessed outcomes.

We did not find any clear evidence from RCTs that isotretinoin improves acne severity compared with standard oral antibiotic and topical treatment when assessed by a decrease in total inflammatory lesion count, but it may slightly improve physician-assessed acne severity. Only one serious adverse event was reported in the isotretinoin group, which means we are uncertain of the risk of serious adverse effects; however, isotretinoin may result in increased minor adverse effects.

Heterogeneity in the studies comparing different regimens, doses, or formulations of oral isotretinoin meant we were unable to undertake meta-analysis. Daily treatment may be more effective than treatment for one week each month. None of the randomised studies in this comparison reported serious adverse effects, or measured improvement in acne severity assessed by physician's global evaluation. We are uncertain if there is a difference in number of minor adverse effects, such as skin dryness, between doses/regimens.

Evidence quality was lessened due to imprecision and attrition bias. Further studies should ensure clearly reported long- and short term standardised assessment of improvement in total inflammatory lesion counts, participant-reported outcomes, and safety. Oral isotretinoin is a well-established treatment for severe acne, and for acne that has not responded to oral antibiotics plus topical agents.

The clinical trial evidence for oral isotretinoin conducted around 30 years ago was low quality. Further trials are needed to evaluate different dose/regimens of oral isotretinoin in acne of all severities.

3.3 Systematische Reviews

Kim JE et al., 2018 [3].

Comparison of the efficacy of Azithromycin versus Doxycycline in acne vulgaris: a meta-analysis of randomized controlled trials

Fragestellung

We performed a meta-analysis of randomized controlled trials (RCTs) that compared the efficacy of oral azithromycin pulse therapy with that of oral daily doxycycline in the management of moderate to severe acne vulgaris.

Methodik

Population:

- patients with moderate to severe acne vulgaris

Intervention:

- azithromycin,"

Komparator:

- doxycycline

Endpunkte:

- Remaining acne lesion counts, patients' self-assessment of treatment, and the investigators' assessment of treatment after 12 weeks

Recherche/Suchzeitraum:

- A search was conducted of five scientific databases (MEDLINE, EMBASE, Cochrane Library, SCOPUS, and Web of Science) until December 2016.

Qualitätsbewertung der Studien:

- The Cochrane Collaboration's risk of bias tool was used to assess the risk of bias in all included studies.

Ergebnisse

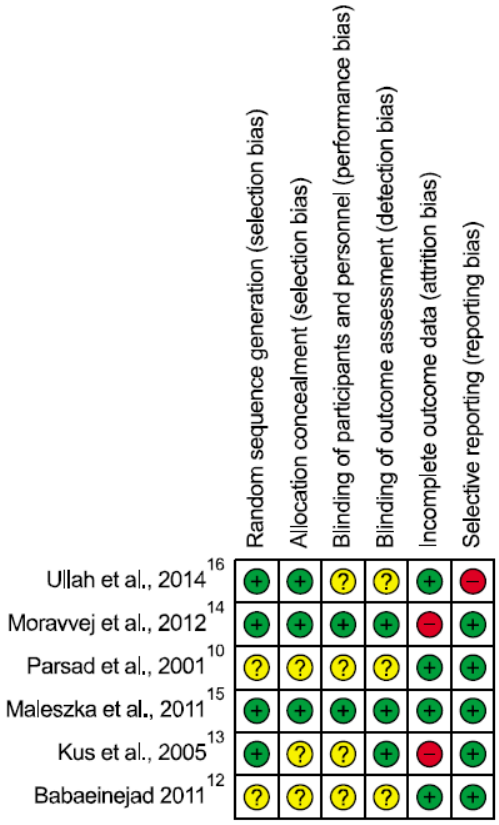
Anzahl eingeschlossener Studien:

- 6 RCT, 906 patients

Charakteristika der Population:

- patients with moderate to severe acne vulgaris
- of the six studies, two were performed in Iran and one each was performed in India, Turkey, Poland, and Pakistan.

Qualität der Studien:



Supplementary Fig. 1. Risk of bias assessment of the included studies.

Studienergebnisse:

- At 12 weeks, remaining inflammatory and non-inflammatory acne lesion profiles were similar in the azithromycin pulse therapy and doxycycline daily therapy groups, with no significant difference between groups and no heterogeneity
- meta-analysis of patients' self-assessment data from two studies revealed no significant difference between groups and moderate heterogeneity
- meta-analysis of investigators' assessment of treatment in all six studies; the analysis showed no significant difference between groups in both excellent and moderate response

Fazit der Autoren

This study indicates that azithromycin pulse therapy is equivalent to doxycycline at 12 weeks in the efficacy of the treatment for moderate to severe acne vulgaris Therefore, oral azithromycin pulse therapy may be a good alternative to doxycycline in the management of acne for those unable to tolerate doxycycline.

Vallerand IA et al., 2018 [7].

Efficacy and adverse events of oral isotretinoin for acne: a systematic review

Fragestellung

The objective of this systematic review was to summarize results from all available randomized clinical trials on oral isotretinointo compare its clinical efficacy and adverse event profilewith placebo or alternative therapies.

Methodik

Population:

- Patients with acne

Intervention:

- isotretinoin

Komparator:

- Placebo or other therapy

Endpunkte:

- primary outcome of interest was treatment efficacy of oral isotretinoin, classified as change in acne lesion counts where possible[1]
- Secondary outcomes in this review included adverse events from acne therapy

Recherche/Suchzeitraum:

- MEDLINE, Embase and Cochrane Central databases using key words related to acne and isotretinoin without language restrictions, and manually searched study reference lists and clinical trial registries up to 18 October 2016

Qualitätsbewertung der Studien:

- Study quality was assessed by the same two authors using the Cochrane Collaboration's Risk of Bias Assessment Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 trials

Charakteristika der Population:

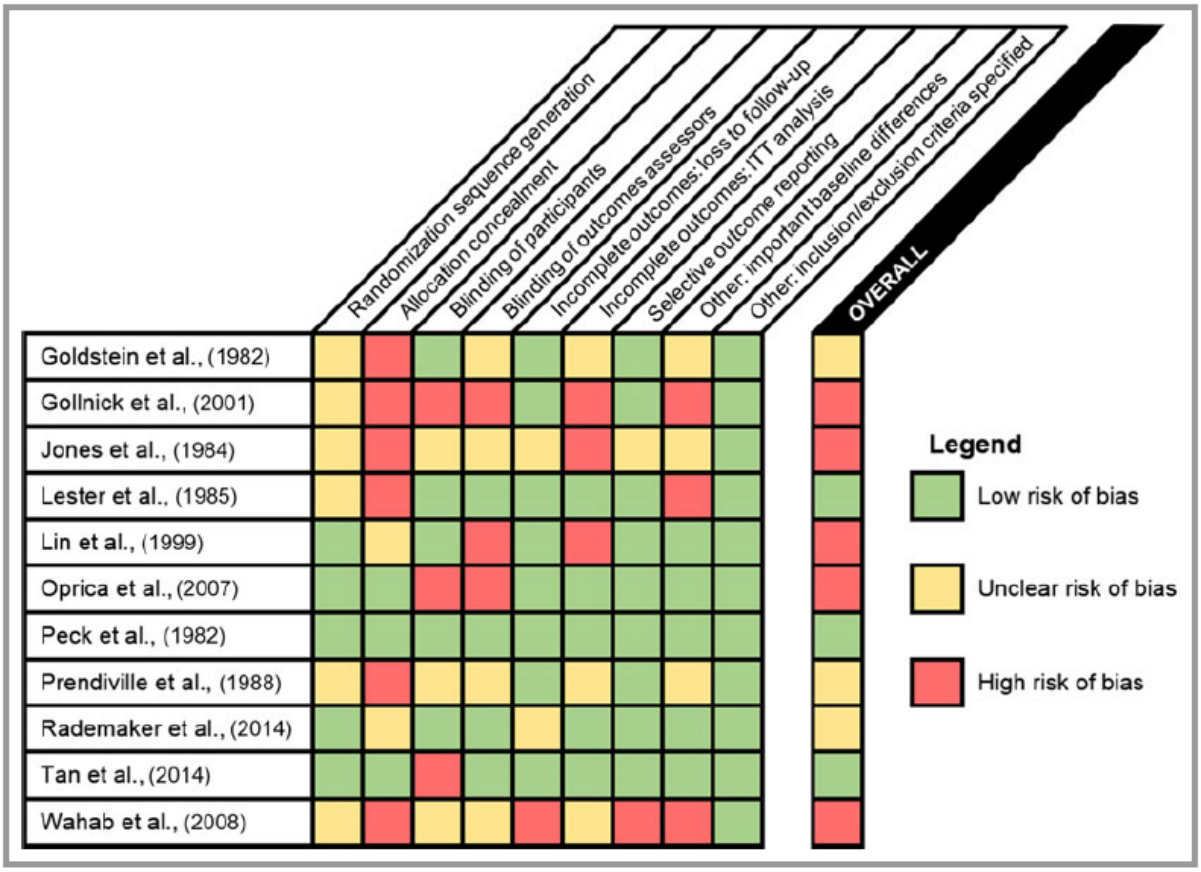
- participants generally had moderate-to-severe acne
- total 760 patients randomized containing mostly men, only 156 were female
- Mean treatment ages ranged from 18 to 47.9 years

[1] To establish the clinical relevance of statistical tests, the recommendation from the Canadian clinical practice guideline on acne was used, where clinical relevance is defined as a reduction in acne lesion counts by > 10%.[10,20]

Qualität der Studien:

- Only one study was classified as having a low risk of bias across all nine criteria considered in study quality

By focusing on only the criteria with the greatest influence on efficacy and adverse event outcomes, three studies were classified as having an overall low risk of bias, three had anunclear risk of bias and five had a high risk of bias



Studienergebnisse:

- Oral antibiotic control
  - Seven trials were performed with oral antibiotic comparators, comprising 593 participants randomized (304 in the antibiotic control groups)
  - the antibiotics tested against isotretinoin included minocycline (n = 1),[23] erythromycin (n = 1),[24,25] tetracycline (n = 2),[26,28] dapsone (n = 1),[30] doxycycline (n = 1)[32] and azithromycin (n = 1).[33]
  - In each of these trials, isotretinoin reduced acne severity more than oral antibiotic therapy; however, this was statistically significant for only three of seven antibiotics trials.
  - These studies generally had similar participant ages (means of 18–24 years), extended treatment durations (16–24 weeks) and patients with severe acne at baseline based on lesion counts or grading scales
- Other control

- In the remaining two trials, one was performed with an alternative retinoid comparator (etretinate),[22] and the other with a vitamin B complex comparator, for a total of 76 participants randomized (38 in the control groups).[27]
- In both the vitamin B and etretinate studies, isotretinoin reduced acne severity more than control, and this difference was statistically significant. Importantly, the vitamin B trial was conducted on an older population with chronic kidney disease who were being treated concurrently with dialysis.

Fazit der Autoren

This review provides support that oral isotretinoin can reduce acne lesion counts to a greater extent than control interventions. However, adverse events are more frequently seen with oral isotretinoin than with control, and may be more likely to occur at higher daily doses. Most isotretinoin adverse events are minor dryness-related skin symptoms, whereas adverse events from isotretinoin causing participant withdrawal from trials were limited to 3.2% of patients randomized to isotretinoin. These included Stevens–Johnson syndrome, severe cheilitis, severe xerosis, severe acne flare, photosensitivity, elevated liver enzymes, decreased appetite, headache and depressed mood. Consequently, the Canadian, American and European clinical guidelines on acne are well supported by this review.

3.4 Leitlinien

Le Cleach L et al., 2017 [4].

Guidelines for the management of acne: recommendations from a French multidisciplinary group

Leitlinienorganisation/Fragestellung

These are the updated French best practice guidelines initially released in 2007.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Literature search conducted on 28 July 2016; last search September 2014

LoE und GoR

Table 1 Recommendation grades according to the French National Authority for Health for clinical practice guidelines[5]

Level of evidence (from the literature)	Grade
Level 1 Powerful randomized comparative trials Meta analysis of randomized comparative trials Decision analysis based on well conducted studies	A Established scientific evidence
Level 2 Less powerful randomized comparative trials Well conducted nonrandomized comparative studies Cohort studies	B Scientific presumption
Level 3 Case–control studies	C Low level of evidence

Level 4 Comparative studies with considerable bias Retrospective studies Case series	C Low level of evidence
If no data are available, recommendations are based on consensus among Working Group members after consulting the External Review Group. Absence of gradation does not mean that these recommendations are not adequate or useless. However, they must encourage further studies	Consensual Working Group opinion (CWGO)

Sonstige methodische Hinweise

- risk of bias using Appraisal of Guidelines for REsearch & Evaluation (AGREE)8 for guidelines, Assessing Methodological quality for SysTemAtic Reviews (AMSTAR)9 for systematic reviews and the Risk-of-Bias tool for randomized controlled trials (Cochrane collaboration)

Empfehlungen (siehe Abbildung 2)

Specific recommendations for systemic treatments

Antibiotics

In light of the low level of evidence of antibiotic efficacies and the risk of inducing bacterial resistance to those drugs, the indication of topical antibiotics has been limited (Fig. 1). They must always be combined with a topical agent (benzoyl peroxide, retinoid or azelaic acid). Oral lymecycline or doxycycline prescriptions should always be limited to 3 months and combined with topical treatment. In light of the low level of evidence of oral erythromycin efficacy [no trial vs. placebo, four randomized controlled superiority trials vs. active comparator (doxycycline, n = 1, tetracycline, n = 3), of which none found a statistically significant difference between groups] and the high level of resistance of some bacterial species to it, use of this antibiotic must be limited to cases with profoundly affected quality of life, contraindication to cyclines and failure of well-administered topical treatment. Other systemic antibiotics have no indication to treat acne.

Hormonal Therapy

When birth control is not required, combined oestrogen–progestin oral contraceptives are not indicated to treat acne. If a contraceptive method is needed, the prescription of combined oestrogen–progestin contraception should be assessed in terms of the risk/benefit ratio, notably the relative risk of thromboembolic events according to type of associated progestin. A combined oestrogen–progestin contraceptive containing levonorgestrel is recommended as first-line therapy, with norgestimate as the second-line choice. If acne persists despite dermatological treatments (topical treatments or systemic antibiotics), other hormonal

treatments, including cyproterone acetate/ethinylestradiol (2 mg/0035 mg), should be considered as an alternative.

Isotretinoin

Isotretinoin is recommended as second-line treatment for moderate to severe acne and as first-line treatment for very severe acne… Before starting isotretinoin, the patient and his/her family circle must be informed of the potential risk of psychiatric disorders and the patient's treating physician must be notified of any mood or behaviour change… The WG consensus concluded that evidence was too weak to support sequential (1 week or 10 consecutive days per month) or low-dose isotretinoin [< 0.5 mg kg-1 (0.25– 0.4 mg kg-1)].

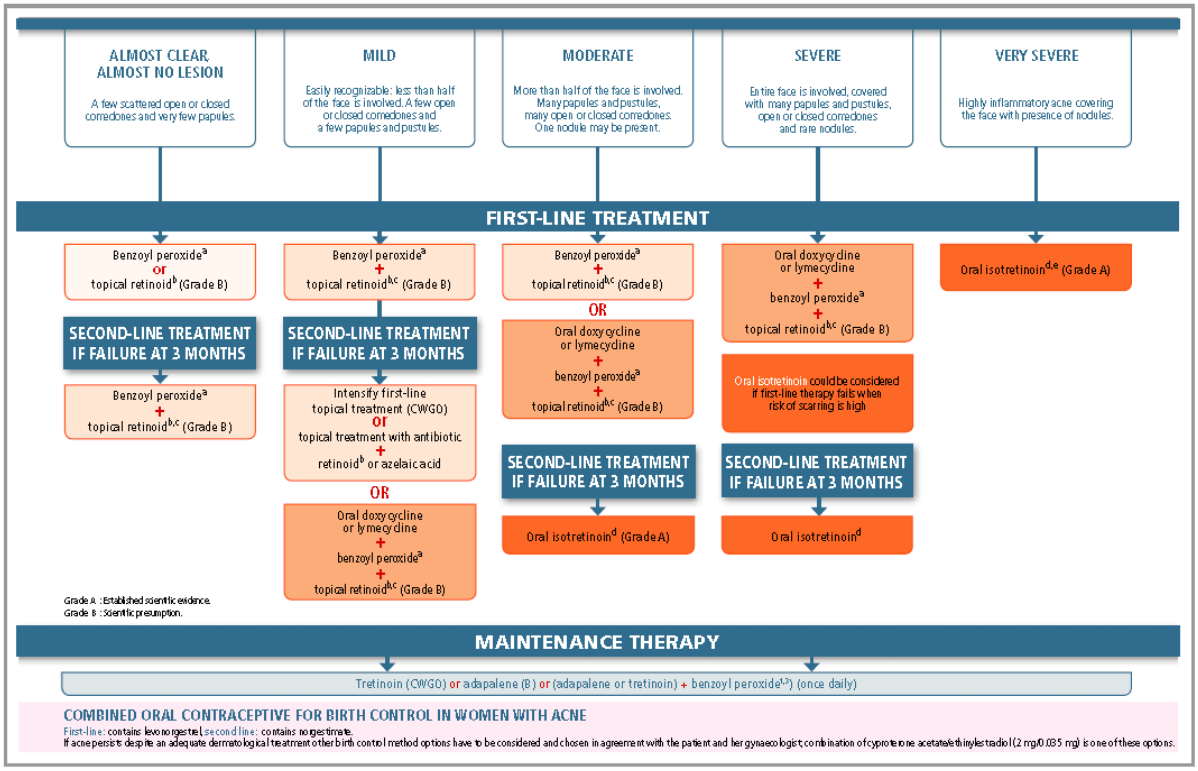


Abbildung 2: French guidelines for acne management: treatment algorithm for acne in adults and adolescents, Le Cleach et al. [4]

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Asai Y et al., 2016 [1].

Management of acne: Canadian clinical practice guideline

Fragestellung

The recommendations in this guideline address acne vulgaris in pediatric and adult age groups, with the following exclusions: neonatal, infantile and late-onset acne; acne fulminans; acne

inversa (hidradenitis suppurativa); and acne variants such as gram-negative folliculitis, rosacea, demodicidosis, pustular vasculitis, mechanical acne, oil or tar acne, and chloracne.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;

Recherche/Suchzeitraum:

- Update Recherche von 03/2010 bis 07/2015

LoE

Box 1: Grading of evidence[16]

Grading of included studies

A. Randomized, double-blind clinical trial of high quality (e.g., sample-size calculation, flow chart of patient inclusion, intention-to-treat analysis, sufficient sample size)

B. Randomized clinical trial of lesser quality (e.g., only single-blind; limited sample size, but with at least 15 patients per study arm)

C. Comparative trial with severe methodologic limitations (e.g., not blinded, very small sample size, no randomization)

Grading of evidence for treatment efficacy

- Level 1: Further research is unlikely to change confidence in the estimate of effect (i.e., at least two grade A trials are available, and their results are largely consistent with results of additional grade B or grade C studies)
- Level 2: Further research is likely to have an important effect on confidence in the estimate of effect and may change the estimate (i.e., at least three grade B trials are available, and their results are largely consistent with any additional grade C trials)
- Level 3: Further research is very likely to have an important effect on confidence in the estimate of effect and is likely to change the estimate (i.e., conflicting evidence or limited number of trials, mostly grade B or grade C)
- Level 4: Any estimate of effect is very uncertain (i.e., little or no systematic experimental evidence; trials extremely limited in number and/or quality)

GoR

Box 2: Strength of recommendations* and clinical interpretation†

- High strength: action strongly recommended; definitely use
- Medium strength: action can be recommended; definitely use if a higher-strength recommendation is not available or appropriate
- Low strength: action may be considered; consider if a higher-strength recommendation is not available or appropriate
- Negative strength: action not recommended; do not use
- Open strength: recommendation for or against the action cannot be made at this time; each practitioner must consider the benefit–harm ratio for use on a case-by-case basis

*Efficacy, safety, level of evidence and patient preference were considered in determining the strength of recommendations.
†In accordance with methods for the European Evidence-Based (S3) Guidelines for the Treatment of Acne,[16] a threshold effect size of 10% difference between treatments was considered clinically relevant.

Sonstige methodische Hinweise

- Die LL wurde nach dem AGREEII-Instrument und dem ADAPTE-Framework zur Anpassung von Leitlinien entwickelt

Empfehlungen

(siehe auch Anhang, Abbildung 3)

Empfehlung Comedonal Acne

- For comedonal acne, we recommend topical retinoids or benzoyl peroxide (medium-strength recommendation; confidence in effect estimate is moderate). (Ref. 16-30)
- For comedonal acne, we recommend the fixeddose combinations adapalene–benzoyl peroxide and clindamycin–benzoyl peroxide (mediumstrength recommendation; confidence in effect estimate is moderate). (Ref. 16)
- For comedonal acne, the combination of clindamycin 1.2% and tretinoin 0.025% (as a gel) and, for women, combined oral contraceptives may be considered (low-strength recommendation; confidence in effect estimate is low). (Ref. 31,32)

Empfehlung Localized mild-to-moderate papulopustular acne

- For localized mild-to-moderate papulopustular acne, we strongly recommend benzoyl peroxide as monotherapy (high-strength recommendation; confidence in effect estimate is high). (Ref. 16, 22)
- For localized mild-to-moderate papulopustular acne, we strongly recommend topical retinoids as monotherapy (high-strength recommendation; confidence in effect estimate is high). (Ref. 16, 23-30, 33
- For localized mild-to-moderate papulopustular acne, we strongly recommend the fixed-dose combination of clindamycin 1% and benzoyl peroxide 5% and the fixed-dose combination of adapalene 0.1% and benzoyl peroxide 2.5% (as gels) (high-strength recommendation; confidence in effect estimate is high). (Ref. 16)

- For localized mild-to-moderate papulopustular acne, the combination of clindamycin 1.2% and tretinoin 0.025% gel may be considered (low strength recommendation; confidence in effect estimate is low). (Ref. 31)

Empfehlung Extensive moderate papulopustular acne

- For more extensive moderate papulopustular acne, we recommend addition of systemic antibiotics to the topical medications above, as recommended for mild-to-moderate papulopustular acne (medium-strength recommendation; confidence in effect estimate is moderate). (Ref. 16, 34)
- For more extensive moderate papulopustular acne in women, we recommend addition of combined oral contraceptives to the topical medications above, as recommended for mild to-moderate papulopustular acne (medium strength recommendation: confidence in effect estimate is moderate). (Ref. 35-41)

Empfehlung Severe acne

- For severe acne, we strongly recommend the use of oral isotretinoin (high-strength recommendation; confidence in effect estimate is high). (Ref. 16)
- For severe acne, we recommend the use of systemic antibiotics in combination with benzoyl peroxide, with or without topical retinoids (medium-strength recommendation; confidence in effect estimate is moderate). (Ref. 42, 43)

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Nast A et al., 2016 [5]. (siehe auch [6])

European Academy of Dermatology and Venereology/European Dermatology Forum (EDF)

European evidence-based (S3) guideline for the treatment of acne - update 2016

Fragestellung

Treatment of acne

Methodik

Grundlage der Leitlinie

- Update der LL-Version von 2011
- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist vereinzelt dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert; gültig bis 31. Dezember 2020

Recherche/Suchzeitraum:

- MEDLINE, MEDLINE In-Process and EMBASE (via OvidSP) were systematically searched. For topical and systemic treatments, the search covered 2010 to 5th July 2015. The inception dates were determined by the literature search periods covered in the previous EU Acne Guideline.

LoE

- According to GRADE

Table 2 Generation of level of evidence

Level of evidence	Number of studies with specific grade of evidence
Summary of efficacy:	
1	At least 2 A studies
2	At least 1 A study and 1 B study
3	At least 1 A study
4	Less than 1 A study
Summary of safety/tolerability:	
1	At least 3 A studies
2	At least 2 A studies and 1 B study
3	At least 2 A studies
4	Less than 2 A studies

GoR

Strength of recommendation

In order to grade the recommendation a "standardized guideline" language was used:

1 is strongly recommended
2 can be recommended
3 can be considered
4 is not recommended
5 may not be used under any circumstances
6 a recommendation for or against treatment X cannot be made at the present time

Sonstige methodische Hinweise

- keine

Empfehlungen

Treatment of comedonal acne

Recommendations for comedonal acne [1]

High strength of recommendation

None

Medium strength of recommendation

Topical retinoids [2] can be recommended for the treatment of comedonal acne.

Low strength of recommendation

Azelaic acid can be considered for the treatment of comedonal acne.

BPO can be considered for the treatment of comedonal acne.

Open recommendation

A recommendation for or against treatment of comedonal acne with visible light as monotherapy, lasers with visible wavelengths and lasers with infrared wavelengths, with intense pulsed light (IPL) and photodynamic therapy (PDT) cannot be made at the present time.

Negative recommendation

Topical antibiotics are not recommended for the treatment of comedonal acne.

Hormonal anti-androgens, systemic antibiotics and/or systemic isotretinoin are not recommended for the treatment of comedonal acne.

Artificial ultraviolet (UV) radiation is not recommended for the treatment of comedonal acne.

[1] Limitations can apply that may necessitate the use of a treatment with a lower strength of recommendation as a first line therapy (e.g. financial resources/reimbursement limitations, legal restrictions, availability, drug licensing).

[2] Adapalene to be preferred over tretinoin/isotretinoin (see chapter 5.4.1 in long version).

Treatment of populopustular acne

Recommendations for mild to moderate papulopustular acne [1]

High strength of recommendation

The fixed-dose combination adapalene and BPO is strongly recommended for the treatment of mild to moderate papulopustular acne.

The fixed-dose combination BPO and clindamycin [2] is strongly recommended for the treatment of mild to moderate papulopustular acne.

Medium strength of recommendation

Azelaic acid can be recommended for the treatment of mild to moderate papulopustular acne.

BPO can be recommended for the treatment of mild to moderate papulopustular acne.

A combination of a systemic antibiotic [2,3,4] with adapalene [5] can be recommended for the treatment of moderate papulopustular acne. [6]

The fixed-dose combination clindamycin and tretinoin [2] can be recommended for the treatment of mild to moderate papulopustular acne.

Topical retinoids [7] can be recommended for the treatment of mild to moderate papulopustular acne.

Low strength of recommendation

Blue light monotherapy can be considered for the treatment of mild to moderate papulopustular acne.

Oral zinc can be considered for the treatment of mild to moderate papulopustular acne.

Systemic antibiotic [2,3,4] in combination with azelaic acid [8] can be considered for the treatment of mild to moderate papulopustular acne.

A combination of a systemic antibiotic [2,3,4] with adapalene in fixed-dose combination with BPO [9] can be considered for the treatment of moderate papulopustular acne.

A combination of a systemic antibiotic [2,3,4] with BPO [10] can be considered for the treatment of moderate papulopustular acne.

The fixed-dose combination of erythromycin and isotretinoin [2] can be considered for the treatment of mild to moderate papulopustular acne.

The fixed-dose combination of erythromycin and tretinoin [2] can be considered for the treatment of mild to moderate papulopustular acne.

Open recommendation

Due to a lack of sufficient evidence, a recommendation for or against treatment of mild to moderate papulopustular acne with red light, IPL, Laser or PDT cannot be made at the present time.

Negative recommendation

Topical antibiotics as monotherapy are not recommended for the treatment of mild to moderate papulopustular acne.

Artificial UV radiation is not recommended for the treatment of mild to moderate papulopustular acne.

The fixed-dose combination of erythromycin and zinc is not recommended for the treatment of mild to moderate papulopustular acne.

Systemic therapy with anti-androgens, antibiotics, and/or isotretinoin is not recommended for the treatment of mild to moderate papulopustular acne.

[1] Limitations can apply that may necessitate the use of a treatment with a lower strength of recommendation as a first line therapy (e.g. financial resources/re-imbursement limit, legal restrictions, availability, drug licensing).

[2] Prescribers of antibiotics should be aware of the potential risk of the development of antibiotic resistances.

[3] Doxycycline and lymecycline (see chapter 5.4.2 in long version), limited to a treatment period of 3 months.

[4] In case of more widespread disease/moderate severity, initiation of a systemic treatment can be recommended.

[5] Only studies found on systemic AB + adapalene; isotretinoin and tretinoin can be considered for combination treatment based on expert opinion.

[6] The f.c. of clindamycin/tretinoin shows comparable efficacy and safety to the f.c. of BPO/clindamycin; downgrading to a medium strength of recommendation was done based on general concerns with respect to the development of antibiotic resistance.

[7] Adapalene to be preferred over tretinoin/isotretinoin (see chapter 5.4.1 in long version).

[8] Indirect evidence from nodular and conglobate acne and expert opinion.

[9] Indirect evidence from severe papulopustular acne.

[10] Indirect evidence from a study also including chlorhexidin, recommendation additionally based on expert opinion.

Recommendations for severe papulopustular/moderate nodular acne [1]

High strength of recommendation
Oral isotretinoin monotherapy is strongly recommended for the treatment of severe papulopustular/moderate nodular acne.
Medium strength of recommendation
Systemic antibiotics [2,3] in combination with adapalene [4], with the fixed-dose combination of adapalene and BPO, or in combination with azelaic acid [5] can be recommended for the treatment of severe papulopustular/moderate nodular acne.
Low strength of recommendation
Systemic antibiotics [2,3] in combination with BPO [5] can be considered for the treatment of severe papulopustular/moderate nodular acne.
For females: Hormonal anti-androgens in combination with systemic antibiotic [2,3] and topicals (apart from antibiotics) can be considered for the treatment of severe papulopustular/moderate nodular acne.
For females: Hormonal anti-androgens in combination with a topical treatment (apart from antibiotics) can be considered for the treatment of severe papulopustular/moderate nodular acne.
Open recommendation
Due to a lack of sufficient evidence, a recommendation for or against treatment of severe papulopustular/moderate nodular acne with red light, IPL, laser or PDT cannot be made at the present time.
Although PDT is effective in the treatment of severe papulopustular/moderate nodular acne, a recommendation for or against its use cannot be made at the present time due to a lack of standard treatment regimens that ensure a favourable profile of acute adverse reaction.
Negative recommendation
Single or combined topical monotherapy is not recommended for the treatment of severe papulopustular/moderate nodular acne.
Oral antibiotics as monotherapy are not recommended for the treatment of severe papulopustular/moderate nodular acne.
Oral anti-androgens as monotherapy are not recommended for the treatment of severe papulopustular/moderate nodular acne.
Visible light as monotherapy is not recommended for the treatment of severe papulopustular/moderate nodular acne.
Artificial UV radiation sources are not recommended as a treatment of severe papulopustular/moderate nodular acne.

[1]Limitations can apply that may necessitate the use of a treatment with a lower strength of recommendation as a first line therapy (e.g. financial resources/re-imbursement limit, legal restrictions, availability, drug licensing).
[2]Prescribers of antibiotics should be aware of the potential risk of the development of antibiotic resistances.
[3]Doxycycline and lymecycline (see chapter 5.4.2 in long version), limited to a treatment period of 3 months
[4]Only studies found on systemic AB + adapalene; isotretinoin and tretinoin can be considered for combination treatment based on expert opinion.
[5]Indirect evidence from nodular and conglobate acne and expert opinion.
[6]Indirect evidence from a study also including chlorhexidin, recommendation additionally based on expert opinion.

Treatment of nodular/conglobate acne

Recommendations for severe nodular/conglobate acne[1]

High strength of recommendation
Oral isotretinoin is strongly recommended as a monotherapy for the treatment of severe nodular/conglobate acne.
Medium strength of recommendation
Systemic antibiotics [2,3] in combination with the fixed-dose combination of adapalene and BPO or in combination with azelaic acid can be recommended for the treatment of severe nodular/conglobate acne.
Low strength of recommendation
Systemic antibiotics [2,3] in combination with adapalene [4,5] or BPO [5] can be considered for the treatment of severe nodular/conglobate acne.
For females: Hormonal anti-androgens in combination with systemic antibiotic [2,3] and topicals (apart from antibiotics) can be considered for the treatment of severe nodular/conglobate acne.
For females: Hormonal anti-androgens in combination with a topical treatment can be considered for the treatment of severe nodular/conglobate acne.
Open recommendation
Due to a lack of sufficient evidence, it is currently not possible to make a recommendation for or against treatment with IPL or laser in severe nodular/conglobate acne.
Although PDT is effective in the treatment of severe nodular/conglobate acne, it cannot yet be recommended due to a lack of standard treatment regimens that ensure a favourable profile of acute adverse reaction.
Negative recommendation
Topical monotherapy is not recommended for the treatment of conglobate acne.
Oral antibiotics are not recommended as monotherapy for the treatment of severe nodular/conglobate acne.
Oral anti-androgens are not recommended as monotherapy for the treatment of severe nodular/conglobate acne.
Artificial UV radiation sources are not recommended for the treatment of severe nodular/conglobate acne.
Visible light as monotherapy is not recommended for the treatment of severe nodular/conglobate acne.

[1]Limitations can apply that may necessitate the use of a treatment with a lower strength of recommendation as a first line therapy (e.g. financial resources/re-imbursement limit, legal restrictions, availability, drug licensing).
[2]Prescribers of antibiotics should be aware of the potential risk of the development of antibiotic resistances.
[3]Doxycycline and lymecycline (see chapter 5.4.2 in long version), limited to a treatment period of 3 months.
[4]Only studies found on systemic AB + adapalene; isotretinoin and tretinoin can be considered for combination treatment based on expert opinion.
[5]Indirect evidence from severe papulopustular acne.

Maintenance therapy

Recommendations for maintenance therapy
High strength of recommendation
None
Medium strength of recommendation
None
Low strength of recommendation
Comedonal acne
Azelaic acid can be considered for the maintenance treatment of comedonal acne.
Topical retinoid [1] can be considered for the maintenance treatment of comedonal acne
Mild to moderate papulopustular acne
Azelaic acid can be considered for the maintenance treatment of mild to moderate papulopustular acne.
Topical retinoid [1] can be considered for the maintenance treatment of mild to moderate papulopustular acne.
Severe papulopustular/moderate nodular acne and severe nodular/conglobate acne
The fixed-dose combination adapalene and BPO [2] can be considered for the maintenance treatment of severe papulopustular/moderate nodular acne and severe nodular/conglobate acne.
Azelaic acid can be considered for the maintenance treatment of severe papulopustular/moderate nodular acne and severe nodular/conglobate acne.
BPO [2] can be considered for the maintenance treatment of severe papulopustular/moderate nodular acne and severe nodular/conglobate acne.
Low dose systemic isotretinoin (max. 0.3 mg/kg/day) can be considered for the maintenance treatment of severe papulopustular/moderate nodular acne and severe nodular/conglobate acne.
Topical retinoid [1] can be considered for the maintenance treatment of severe papulopustular/moderate nodular acne and severe nodular/conglobate acne.
For females: Continued hormonal anti-androgens [3] and topical treatment (apart from antibiotics) can be considered for the maintenance treatment of severe papulopustular/moderate nodular acne and severe nodular/conglobate acne.
Open recommendation
Due to a lack of sufficient evidence, it is currently not possible to make a recommendation for or against maintenance treatment with red light, blue light, IPL, laser, PDT or oral zinc.
Negative recommendation
Topical and/or systemic antibiotics as monotherapy or combination therapy are not recommended for maintenance treatment of acne.
Artificial UV radiation is not recommended for maintenance treatment of acne.

[1] Preference for adapalene over isotretinoin/tretinoin.
[2] In case of continuing inflammatory lesions.
[3] Refer to national guidelines and EMA recommendations for precautions with respect to risk and duration of hormonal anti-androgens/combined oral contraceptives.

Zaenglein AL et al., 2016 [8].

American Academy of Dermatology/ American Academy of Dermatology Association

Guidelines of care for the management of acne vulgaris

Leitlinienorganisation/Fragestellung

This guideline addresses the management of adolescent and adult patients who present with acne vulgaris (AV). This document will discuss various acne treatments, including topical therapies, systemic agents, and physical modalities, including lasers and photodynamic therapy.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und Reviewprozess dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- systematic search of PubMed and the Cochrane Library database from May 2006 through September 2014

LoE

- Evidence was graded using a 3-point scale based on the quality of methodology and the overall focus of the study:

> I. Good-quality patient-oriented evidence (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life).
> II. Limited-quality patient-oriented evidence.
> III. Other evidence, including consensus guidelines, opinion, case studies, or disease-oriented evidence (ie, evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

GoR

- available evidence was evaluated using a unified system called the Strength of Recommendation Taxonomy (SORT) developed by editors of the US family medicine and primary care journals (ie, American Family Physician, Family Medicine, Journal of Family Practice, and BMJ USA):

> Clinical recommendations were developed on the best available evidence tabled in the guideline. The strength of recommendation was ranked as follows:
> A. Recommendation based on consistent and good-quality patient-oriented evidence.
> B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.
> C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence.

Sonstige methodische Hinweise

- keine

Empfehlungen

	Mild	Moderate	Severe
1st Line Treatment	Benzoyl Peroxide (BP) or Topical Retinoid -or- Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic	Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- Oral Antibiotic + Topical Retinoid + BP -or- Oral Antibiotic + Topical Retinoid + BP + Topical Antibiotic	Oral Antibiotic + Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- Oral Isotretinoin
Alternative Treatment	Add Topical Retinoid or BP (if not on already) -or- Consider Alternate Retinoid -or- Consider Topical Dapsone	Consider Alternate Combination Therapy -or- Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin	Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin

Fig 1. Treatment algorithm for the management of acne vulgaris in adolescents and young adults. The *double asterisks* (**) indicate that the drug may be prescribed as a fixed combination product or as separate component. *BP*, Benzoyl peroxide.

Zusammenfassung Empfehlungen

Table III. Strength of recommendations for the management and treatment of acne vulgaris

Recommendation	Strength of recommendation	Level of evidence	References
Grading/classification system	B	II, III	8-39
Microbiologic testing	B	II, III	40-48
Endocrinologic testing	B	I, II	49-56
Topical therapies			
Benzoyl peroxide	A	I, II	57-59
Topical antibiotics (eg, clindamycin and erythromycin)	A	I, II	60-66
Combination of topical antibiotics and benzoyl peroxide	A	I	67-69
Topical retinoids (eg, tretinoin, adapalene, and tazarotene)	A	I, II	70-81
Combination of topical retinoids and benzoyl peroxide/topical antibiotic	A	I, II	75,76
Azelaic acid	A	I	82,83
Dapsone	A	I, II	84-86
Salicylic acid	B	II	87
Systemic antibiotics			
Tetracyclines (eg, tetracycline, doxycycline, and minocycline)	A	I, II	88-91
Macrolides (eg, azithromycin and erythromycin)	A	I	92
Trimethoprim (with or without sulfamethoxazole)	B	II	93,94
Limiting treatment duration and concomitant/maintenance topical therapy	A	I, II	95-97
Hormonal agents			
Combined oral contraceptives	A	I	98-101
Spironolactone	B	II, III	102,103
Flutamide	C	III	104,105
Oral corticosteroids	B	II	106
Isotretinoin			
Conventional dosing	A	I, II	107-133
Low-dose treatment for moderate acne	A	I, II	134-138
Monitoring	B	II	139-142
iPLEDGE and contraception	A	II	143,144
Miscellaneous therapies and physical modalities			
Chemical peels	B	II, III	145-147
Intralesional steroids	C	III	148,149
Complementary and alternative therapies (eg, tea tree oil, herbal, and biofeedback)	B	II	150-156
Role of diet in acne			
Effect of glycemic index	B	II	157-161
Dairy consumption	B	II	162-164

Empfehlung Topische Therapien

Table V. Recommendations for topical therapies

Benzoyl peroxide or combinations with erythromycin or clindamycin are effective acne treatments and are recommended as monotherapy for mild acne, or in conjunction with a topical retinoid, or systemic antibiotic therapy for moderate to severe acne
Benzoyl peroxide is effective in the prevention of bacterial resistance and is recommended for patients on topical or systemic antibiotic therapy
Topical antibiotics (eg, erythromycin and clindamycin) are effective acne treatments, but are not recommended as monotherapy because of the risk of bacterial resistance
Topical retinoids are important in addressing the development and maintenance of acne and are recommended as monotherapy in primarily comedonal acne, or in combination with topical or oral antimicrobials in patients with mixed or primarily inflammatory acne lesions
Using multiple topical agents that affect different aspects of acne pathogenesis can be useful. Combination therapy should be used in the majority of patients with acne
Topical adapalene, tretinoin, and benzoyl peroxide can be safely used in the management of preadolescent acne in children
Azelaic acid is a useful adjunctive acne treatment and is recommended in the treatment of postinflammatory dyspigmentation
Topical dapsone 5% gel is recommended for inflammatory acne, particularly in adult females with acne
There is limited evidence to support recommendations for sulfur, nicotinamide, resorcinol, sodium sulfacetamide, aluminum chloride, and zinc in the treatment of acne

Empfehlung systemische Antibiotika

Table VI. Recommendations for systemic antibiotics

Systemic antibiotics are recommended in the management of moderate and severe acne and forms of inflammatory acne that are resistant to topical treatments
Doxycycline and minocycline are more effective than tetracycline, but neither is superior to each other
Although oral erythromycin and azithromycin can be effective in treating acne, its use should be limited to those who cannot use the tetracyclines (ie, pregnant women or children <8 years of age). Erythromycin use should be restricted because of its increased risk of bacterial resistance
Use of systemic antibiotics, other than the tetracyclines and macrolides, is discouraged because there are limited data for their use in acne. Trimethoprim-sulfamethoxazole and trimethoprim use should be restricted to patients who are unable to tolerate tetracyclines or in treatment-resistant patients
Systemic antibiotic use should be limited to the shortest possible duration. Re-evaluate at 3-4 months to minimize the development of bacterial resistance. Monotherapy with systemic antibiotics is not recommended
Concomitant topical therapy with benzoyl peroxide or a retinoid should be used with systemic antibiotics and for maintenance after completion of systemic antibiotic therapy

Empfehlungen Isotretinoin

Table IX. Recommendations for isotretinoin

Oral isotretinoin is recommended for the treatment of severe nodular acne
Oral isotretinoin is appropriate for the treatment of moderate acne that is treatment-resistant or for the management of acne that is producing physical scarring or psychosocial distress
Low-dose isotretinoin can be used to effectively treat acne and reduce the frequency and severity of medication-related side effects. Intermittent dosing of isotretinoin is not recommended
Routine monitoring of liver function tests, serum cholesterol, and triglycerides at baseline and again until response to treatment is established is recommended. Routine monitoring of complete blood count is not recommended
All patients treated with isotretinoin must adhere to the iPLEDGE risk management program
Females of child-bearing potential taking isotretinoin should be counseled regarding various contraceptive methods including user-independent forms
Prescribing physicians also should monitor their patients for any indication of inflammatory bowel disease and depressive symptoms and educate their patients about the potential risks with isotretinoin

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 5 of 12, May 2019) am 09.05.2019

#	Suchfrage
1	[mh “acne vulgaris”]
2	acne:ti,ab,kw or akne:ti,ab,kw
3	#1 or #2
4	#3 with Cochrane Library publication date from May 2014 to May 2019

Systematic Reviews in Medline (PubMed) am 09.05.2019

#	Suchfrage
1	acne vulgaris[mh]
2	acne[tiab] OR akne[tiab]
3	#1 OR #2
4	(#3) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab]))

	OR (meta[tiab] AND analyt*[tiab])))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
5	((#4) AND ("2014/05/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
6	(#5) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 09.05.2019

#	**Suchfrage**
1	acne vulgaris[mh]
2	acne[tiab] OR akne[tiab]
3	#1 OR #2
4	(#3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
5	(((#4) AND ("2014/05/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
6	(#5) NOT retracted publication[ptyp]

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Anhang

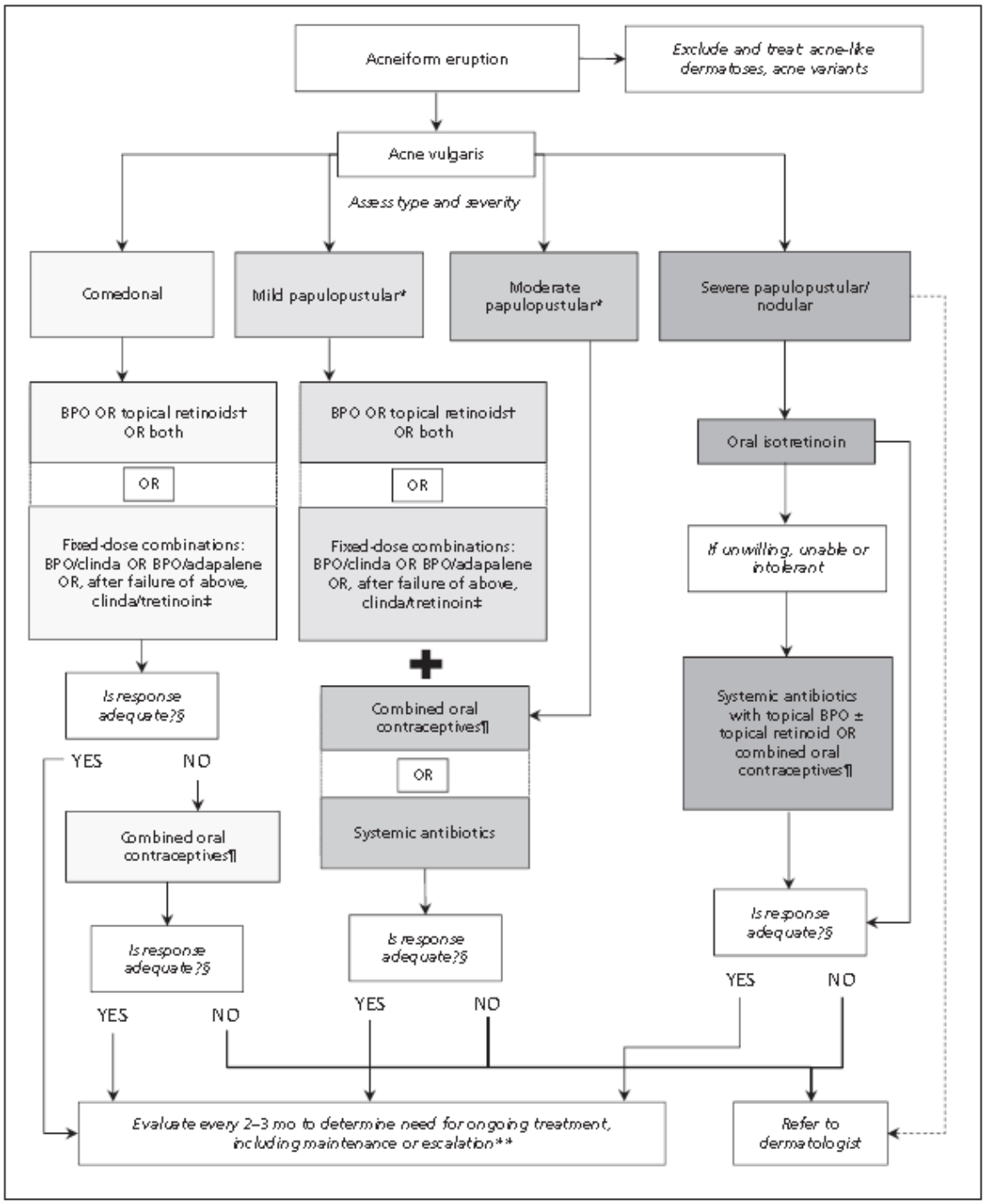

Figure 2: Clinical treatment algorithm for acne. A complete list of recommendations is available in the full guideline (Appendix 4, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.140665/-/DC1). BPO = benzoyl peroxide, clinda = clindamycin, dashed line = optional path. *Blue light and oral zinc may be considered for mild-to-moderate papulopustular acne (low strength of recommendation). †Best evidence is for adapalene and tazarotene. ‡Lower-quality evidence available for clindamycin–tretinoin gel. §Evaluate after 2–3 months. ¶For women only. **Evaluate monthly for isotretinoin.

Abbildung 3: Treatment Algorithim, Asai et al. [1]

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

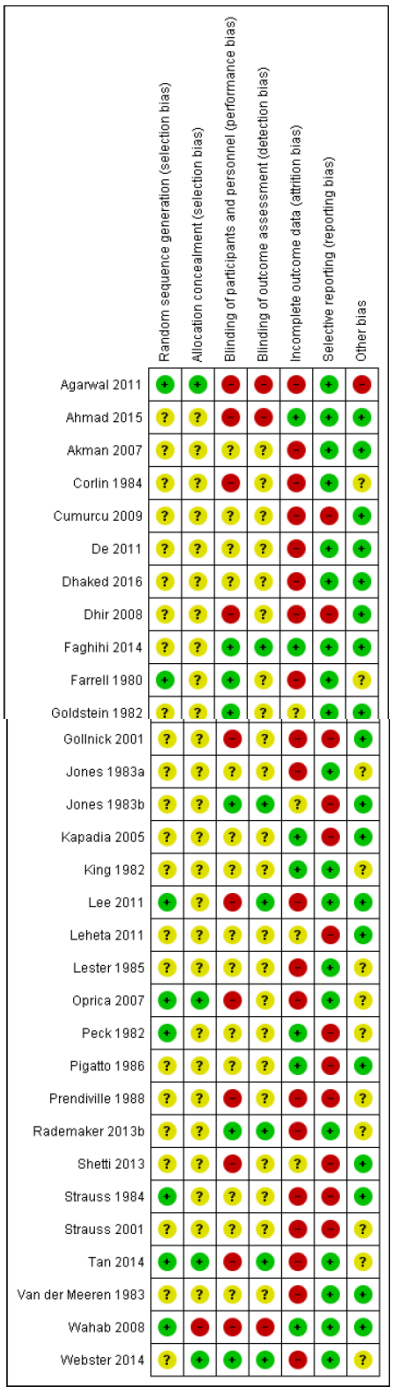

Abbildung 4: Risk of Bias included studies, Costa et al. [2]