NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC) GUIDELINE SYNTHESIS

MANAGEMENT OF ACNE

Guidelines

1. **American Academy of Dermatology (AAD)**. Guidelines of care for acne vulgaris management. J Am Acad Dermatol 2007 Apr;56(4):651-63.
2. **Finnish Medical Society Duodecim (FMSD)**. Acne. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Duodecim Medical Publications Ltd.; 2007 April 4 [Various]
3. **Institute for Clinical Systems Improvement (ICSI)**. Acne management. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2006 May. 33 p. [53 references]

INTRODUCTION:

A direct comparison of American Academy of Dermatology (AAD), Finnish Medical Society Duodecim (FMSD), and Institute for Clinical Systems Improvement (ICSI) recommendations for the management of acne is provided in the tables below. All three organizations rank the level of evidence for each major recommendation.

The FMSD guideline updates its 2006 recommendations, and the ICSI guideline updates its 2003 recommendations.

The ICSI guideline is somewhat broader in scope than the AAD and FMSD guidelines. In addition to addressing management of acne, the ICSI guideline also provides assessment and education recommendations. These topics, however, are beyond the scope of this synthesis.

The tables below provide a side-by-side comparison of key attributes of each guideline, including specific interventions and practices that are addressed. The language used in these tables, particularly that which is used in Table 4, Table 5 and Table 6, is in most cases taken verbatim from the original guidelines:

- Table 1 provides a quick-view glance at the primary interventions considered by each group.
- Table 2 provides a comparison of the overall scope of both guidelines.
- Table 3 provides a comparison of the methodology employed and documented by both groups in developing their guidelines.
- Table 4 provides a more detailed comparison of recommendations offered by each group for the topics under consideration in this synthesis, including:
    - Topical Treatments
    - Oral Antibiotics

    - Oral Retinoids (isotretinoin)
    - Adjunctive Therapies
    - Follow-Up
    - Supporting References
- Table 5 lists the potential benefits and harms associated with the implementation of each guideline as stated in the original guidelines
- Table 6 presents the rating schemes used by AAD, FMSD, and ICSI to rate the level of evidence and/or the strength of the recommendations.

A summary discussion of the areas of agreement and areas of differences among the guidelines is presented following the content comparison tables.

Abbreviations:

- AAD, American Academy of Dermatology
- FMSD, Finnish Medical Society Duodecim
- ICSI, Institute for Clinical Systems Improvement
- OTC, over-the-counter

TABLE 1: COMPARISON OF INTERVENTIONS AND PRACTICES CONSIDERED
("✓" indicates topic is addressed)

	AAD (2007)	FMSD (2007)	ICSI (2006)
Topical treatments	✓	✓	✓
Oral antibiotics	✓	✓	✓
Oral retinoids (isotretinoin)	✓	✓	✓
Adjunctive Therapies	✓	✓	✓
Follow-Up		✓	✓

TABLE 2: COMPARISON OF SCOPE AND CONTENT

Objective and Scope	
AAD (2007)	To address the management of adolescent and adult patients presenting with acne but not the consequences of disease, including the scarring, post-inflammatory erythema, or postinflammatory hyperpigmentation
FMSD	Evidence-Based Medicine Guidelines collect, summarize, and update the

(2007)	core clinical knowledge essential in general practice. The guidelines also describe the scientific evidence underlying the given recommendations.
ICSI (2006)	• To improve the selection of appropriate treatment for patients with acne based on severity • To increase the number of patients who report satisfaction with the treatment of their acne • To increase the number of patients with appropriate follow up for acne treatment
Target Population	
AAD (2007)	Adolescents and adults with acne vulgaris, i.e., open and/or closed comedones (blackheads and whiteheads) and inflammatory lesions including papules, pustules, or nodules
FMSD (2007)	Patients with acne
ICSI (2006)	All patients with acne vulgaris **Note**: This guideline excludes rosacea and folliculitis.
Intended Users	
AAD (2007)	Physicians
FMSD (2007)	Health Care Providers Physicians
ICSI (2006)	Advanced Practice Nurses Allied Health Personnel Health Care Providers Health Plans Hospitals Managed Care Organizations Nurses

	Physician Assistants Physicians

TABLE 3: COMPARISON OF METHODOLOGY	
Methods Used to Collect/Select the Evidence	
AAD (2007)	• *Searches of Electronic Databases* The following evidence report is available: Guidelines of care for acne vulgaris management. Technical report. American Academy of Dermatology Association. 2007. 69 p. Electronic copies: Not available at this time. Print copies: Available from the AAD, PO Box 4014, Schaumburg, IL 60168-4014, Phone: (847) 330-0230 ext. 333; Fax: (847) 330-1120; Web site: www.aad.org. *Described Process*: A work group of recognized experts was convened to determine the audience for the guidelines, define the scope of the guidelines, and identify nine clinical questions to structure the primary issues in diagnosis and management. An evidence-based model was used and some evidence was obtained by a vendor using a search of MEDLINE and EMBASE databases spanning the years 1970 through 2006. Only English-language publications were reviewed. *Number of Source Documents*: Not stated *Number of References*: 180
FMSD (2007)	• *Hand-searches of Published Literature (Primary Sources)* • *Hand-searches of Published Literature (Secondary Sources)* • *Searches of Electronic Databases* *Described Process*: The evidence reviewed was collected from the Cochrane database of systematic reviews and the Database of Abstracts of Reviews of Effectiveness (DARE). In addition, the Cochrane Library and medical journals were searched specifically for original publications.

	Number of Source Documents: Not stated *Number of References*: 5
ICSI (2006)	• *Searches of Electronic Databases* *Described Process: Not stated* *Number of Source Documents: Not stated* *Number of References: 53*
Methods Used to Assess the Quality and Strength of the Evidence	
AAD (2007)	*Expert Consensus (Committee)* *Weighting According to a Rating Scheme (Scheme Given — refer to Table 6)*
FMSD (2007)	*Weighting According to a Rating Scheme (Scheme Given — refer to Table 6)*
ICSI (2006)	*Weighting According to a Rating Scheme (Scheme Given — refer to Table 6)* *Described Process:* Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system presented below, and are designated as positive, negative, or neutral to reflect the study quality. Refer to Table 6 for rating schemes.
Methods Used to Analyze the Evidence	
AAD (2007)	Systematic Review with Evidence Tables *Described Process*: The 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 (i.e., *American Family Physician*, *Family Medicine*, *Journal of Family Practice*, and *BMJ-USA*). This strategy was supported by a decision of the Clinical Guidelines Task Force in 2005 with some minor modifications for a consistent approach to rating the strength of the evidence of scientific studies. For each intervention within the Clinical Questions, an effort was made

	to identify and present the best evidence regarding its use in the treatment of acne. Studies of clinical measurements of outcome were considered for analysis whether or not the clinical outcome was the primary outcome measured.
FMSD (2007)	*Systematic Review* *Described Process*: Not stated
ICSI (2006)	*Systematic Review with Evidence Tables* *Described Process*: Not stated
Methods Used to Formulate the Recommendations	
AAD (2007)	*Expert Consensus* *Described Process*: Clinical recommendations were developed on the best available evidence tabled in the guidelines and explained further in the companion document *Guideline of Care for Acne Vulgaris Management, Technical Report*.
FMSD (2007)	Not stated
ICSI (2006)	Not stated
Outcomes	
AAD (2007)	• Usefulness, reliability, and sensitivity of acne severity grading scales • Usefulness of endocrinologic and microbiologic testing • Number of lesions • Severity of lesions • Psychological and emotional improvement • Adverse effects of treatment
FMSD (2007)	• Efficacy of treatment • Adverse effects of treatment
ICSI (2006)	• Patient factors such as contributing medical conditions and medications • Severity of acne (presence and quantity of papules, pustules, nodules, cysts, and total lesions) • Quality of life and other psychosocial factors

	• Results/outcome of treatments • Side effects of treatment • Patient compliance and adherence
Financial Disclosures/Conflicts of Interest	
AAD (2007)	Each of the following Work Group Members have served as a consultant, received research support or clinical research grants from the following companies: Dr. Strauss was a consultant and investigator for Roche Laboratories receiving honoraria and grants, and a consultant for Medicis receiving honoraria. Dr. Krowchuk has no relevant conflicts of interest to disclose. Dr. Leyden was a consultant for Stiefel and SkinMedica, receiving honoraria; served on the Advisory Board and was a consultant for Galderma and Obaj, receiving honoraria; was on the Advisory Board and was a consultant and investigator for Connetics, Collagenex, Allergan, and Medicis, receiving honoraria. Dr. Lucky was an investigator for Connetics, Dow, Galderma, Healthpoint, Johnson & Johnson, QLT, and Stiefel, receiving grants and an investigator and consultant for Berlex receiving grants and honoraria. Dr. Shalita was a consultant, investigator, stockholder, and speaker for Allergan, receiving grants and honoraria; a consultant for Bradley/Doak receiving honoraria; served on the Advisory Board and was a consultant for Collagenex, receiving honoraria; was a consultant and investigator for Connetics receiving grants and honoraria; an Advisory Board member, consultant, investigator, and speaker for Galderma receiving grants and honoraria; a consultant, speaker, and stockholder for Medicis receiving honoraria; an Advisory Board member for Ranbaxy receiving honoraria; and a consultant, investigator, and speaker for Stiefel, receiving grants and honoraria. Dr. Siegfried was an investigator for Atrix receiving salary. Dr. Thiboutot served on the Advisory Board and was an investigator and speaker for Allergan and Galderma, receiving honoraria; was on the Advisory Board and was a consultant and investigator for Collagenex receiving honoraria; was on the Advisory Board and was an investigator for Connetics, Dermik, and QLT, receiving honoraria; and was a consultant, investigator, and speaker for Intendis, receiving honoraria. Dr. Van Voorhees served on the Advisory Board and was an

	investigator and speaker for Amgen, receiving grants and honoraria; was an investigator for Astellas, Bristol Myers Squibb, and GlaxoSmithKline, receiving grants; was an Advisory Board Member and investigator for Genentech and Warner Chilcott, receiving grants and honoraria; was on the Advisory Board for Centocor receiving honoraria; was a speaker for Connetics receiving honoraria; and was a stockholder of Merck, owning stock and stock options. Dr. Beutner was an employee of Anacor receiving salary and stock options and a stockholder of Dow Pharmaceutical Sciences receiving stock. Ms. Sieck and Dr. Bhushan have no relevant conflicts of interest to disclose.
FMSD (2007)	None stated
ICSI (2006)	No work group members have potential conflicts of interest to disclose. ICSI's conflict of interest policy and procedures are available for review on ICSI's website at www.icsi.org.

TABLE 4: COMPARISON OF RECOMMENDATIONS FOR THE MANAGEMENT OF ACNE	
Topical Treatments	
AAD (2007)	**<u>Topical Therapy</u>** • Topical therapy is a standard of care in acne treatment. • Topical retinoids are important in acne treatment. • Benzoyl peroxide and combinations with erythromycin or clindamycin are effective acne treatments. • Topical antibiotics (e.g., erythromycin and clindamycin) are effective acne treatments. However, the use of these agents alone can be associated with the development of bacterial resistance. • Salicylic acid is moderately effective in the treatment of acne. • Azelaic acid has been shown to be effective in clinical trials, but its clinical use, compared to other agents, has limited efficacy according to experts. • Data from peer-reviewed literature regarding the efficacy of sulfur, resorcinol, sodium sulfacetamide, aluminum chloride, and zinc are limited. • Employing multiple topical agents that affect different aspects of acne pathogenesis can be useful. However, it is the opinion of the work group that such agents not be applied simultaneously unless

	they are known to be compatible. **Recommendations** *Retinoids* Strength of recommendation = A. Level of evidence = I. References: Christiansen et al., 1974, Chalker et al., 1987; Shalita et al., 1999; Lucky et al., 1998 *Benzoyl Peroxide* Strength of recommendation = A. Level of evidence = I. References: Belknap, 1979; Schutte, Cunliffe, & Forster, 1982; Smith et al., 1980; Mills et al., 1986 *Antibiotics* Strength of recommendation = A. Level of evidence = I. References: Bernstein & Shalita, 1980; Jones & Crumley, 1981; Prince et al., 1981; Lesher et al., 1985; Pochi et al., 1988; Dobson & Belknap, 1980; Mills et al., 2002; Leyden et al., 1987; Becker et al., 1981 *Other Agents* Strength of recommendation = A. Level of evidence = I. References: Zouboulis et al., 2000; Chalker et al., 1983; Tschen et al., 2001; Lookingbill et al., 1997; Hjorth & Graupe, 1989

FMSD (2007)	**Local Treatment**
	
	• Local treatment is usually sufficient for comedonic acne and mild common acne.
	• Wash the skin with soap or antibacterial detergents.
	• Comedonic acne can be treated with
	  • Retinoic acid cream or solution (tretinoin [**A**], isotretinoin [**B**])
	  • Adapalen gel [**C**]
	  • Benzoyl peroxide (3-10%)] [**A**] cream or gel
	  • All above drugs can be irritating at first. Use a low concentration of the active drug initially, and advise the patient to wash the drug away after a few hours. The tolerance of the skin increases with time.
	• Common acne can be treated with
	  • Local antibiotics (e.g., clindamycin solution) [**A**]
	  • Combination gel containing benzoyl peroxide and clindamycin
	  • Ultraviolet light therapy (as a course of 15 treatments added to other treatment) for widespread disease
	• Consider systemic treatment if the effect of local treatment is

	unsatisfactory 2 to 3 months from the onset of treatment.
ICSI (2006)	**Clinical Highlights and Recommendations** • Treatment with both a topical retinoid and a topical antibiotic has been found to be an effective course of treatment. *(Annotation #5 in the original guideline document)* **Topical Treatment of Acne** An example of treatment for mild acne may include benzoyl peroxide, a topical antibiotic or a combination product one to two times daily; or a topical retinoid once daily in addition to the above. See tables in Annotation 5 of the original guideline document for description of medications. **Over-the-counter Topical Products** A wide variety of over-the-counter (OTC) topical products are available to the patient for self-treatment of acne. A complete listing is beyond the scope of this publication. The most common ingredient in OTC products is benzoyl peroxide in concentrations up to 10%*. Salicylic acid in concentrations of 0.5% to 2% is a keratolytic found in many OTC acne products. Products may also contain glycolic acid (an alpha-hydroxy acid), sulfur, or resorcinol. **When evaluating a new patient, it is helpful to know which products they may have tried.** * Many of the expensive acne systems advertised contain benzoyl peroxide and offer no advantages over commercial products. **Benzoyl Peroxide** Benzoyl Peroxide is available without a prescription in products such as Clearasil® and by prescription in the products listed below (refer to the original guideline document). It is also available in combination with antibiotics (see Topical Antibiotics table in the original guideline document.) • Benzoyl peroxide (Benzac®, Brevoxyl, Desquam-X®, PanOxyl®, generics) **Topical Retinoids for Acne** Topical retinoids (see table in the original guideline document for a description of the topical retinoids listed below) increase the turnover of follicular epithelial cells, promote drainage of comedones and inhibit new comedone (blackhead, whitehead) formation. Topical retinoids are

	generally applied in the evening. • Adapalene (Differin®) • Tazarotene (Tazorac®) • Tretinoin (Retin-A® generics) • Tretinoin (Retin - A Micro®) **Azelaic Acid** Azelaic acid is a naturally occurring decarboxylic acid which has been shown to be effective in reducing both inflammatory and non-inflammatory acne lesions. • Azelaic Acid (Azelex®) **Topical Antibiotics for Acne** Propionibacterium acnes (P.acnes) is an anaerobic bacterium present within the pilosebaceous follicles. It is thought that this microorganism plays a role in acne-associated inflammation. The antibiotics used to treat acne have been shown to reduce colonization of P.acnes and may also possess direct anti-inflammatory effects. In vitro resistance of P.acnes to commonly used antibiotics has been increasing but the clinical significance of this is uncertain. However, it has been recommended that antibiotics be used with either topical retinoids or benzoyl peroxide. *Single Drug Products* • Clindamycin (Cleocin T®, Evoclin generics) • Erythromycin (A/T/S®, Erygel® Eryderm®, generics) • Sulfacetamide (Klaron®) *Combination Products* • Benzoyl Peroxide 5% - Clindamycin 1% • Benzoyl Peroxide 5% - Erythromycin 3% • Sulfacetamide 10% - Sulfur 5% **Note**: Refer to the original guideline document for tables providing a description of the topical treatments discussed here. Medications are listed alphabetically. Brand names are included for reference only and are not meant to be all inclusive.
Oral Antibiotics	
AAD (2007)	**<u>Systemic Antibiotics</u>** • Systemic antibiotics are a standard of care in the management of moderate and severe acne and treatment-resistant forms of inflammatory acne.

	• Doxycycline and minocycline are more effective than tetracycline, and there is evidence that minocycline is superior to doxycycline in reducing P acnes. • Although erythromycin is effective, use should be limited to those who cannot use the tetracyclines (i.e., pregnant women or children under 8 years of age because of the potential for damage to the skeleton or teeth). The development of bacterial resistance is also common during erythromycin therapy. • Trimethoprim-sulfamethoxazole and trimethoprim alone are also effective in instances where other antibiotics cannot be used. • Bacterial resistance to antibiotics is an increasing problem. • The incidence of significant adverse effects with antibiotic use is low. However, adverse effect profiles may be helpful for each systemic antibiotic used in the treatment of acne. **Recommendations** *Tetracyclines* Strength of recommendation = A. Level of evidence = I. References: Smith, Chalker, & Wehr, 1976; Gratton et al., 1982; Blaney & Cook, 1976; Miller et al., 1996 *Macrolides* Strength of recommendation = A. Level of evidence = I. References: Skidmore et al., 2003; Gammon et al., 1986; Christian & Krueger, 1975; Stoughton et al., 1980 *Trimethoprim-sulfamethoxazole* Strength of recommendation = A. Level of evidence = I. References: Hersle, 1972

FMSD (2007)	**Systemic Treatment**
	
	• Antibiotics
	  • Tetracycline [**B**] and erythromycin [**A**] are equally effective. The usual dose is 250-500 mg/day for a few months. Six months' treatment with tetracycline or erythromycin 1 g/day is more effective than a shorter treatment with a smaller dose. Do not use tetracyclines in children below 12 years of age.
	  • Local treatment and light therapy can be used simultaneously with systemic treatment.
	  • Local treatment is not sufficient in cystic acne and conglobate acne. Use systemic antibiotics or consider referral to a dermatologist. Pus-containing cysts can be drained by incising them with a large-caliber injection

	needle or narrow-tipped scalpel.
ICSI (2006)	**Topical Treatment and Oral Antibiotics for Acne** An example for moderate/severe acne may include examples listed in annotation 5a (of the original guideline document) with the addition of an oral antibiotic while continuing with the topical treatment. (See tables in annotation 5b of the original guideline document for description of products listed below) *First Line Antibiotics* • Erythromycin (Erytabs®, generics) • Tetracycline • Doxycycline (monohydrate and hyclate salts available) • Minocycline (Minocin®, generics) *Second Line Antibiotics* • Clindamycin (Cleocin®, generics) • Sulfamethoxazole/Trimethoprim (Bactrim®, Septra®, generics) Other antibiotics such as azithromycin are being used in acne but studies are preliminary and concrete recommendations regarding their use cannot be made at this time. *Supporting evidence is of classes: A, C, D, R*
Oral Retinoids (isotretinoin)	
AAD (2007)	**<u>Isotretinoin</u>** • Oral isotretinoin is approved for the treatment of severe recalcitrant nodular acne. • It is the unanimous opinion of the acne workgroup that oral isotretinoin is also useful for the management of lesser degrees of acne that are treatment-resistant or for the management of acne that is producing either physical or psychological scarring. • Oral isotretinoin is a potent teratogen. Because of its teratogenicity and the potential for many other adverse effects, this drug should be prescribed only by those physicians knowledgeable in its appropriate administration and monitoring. • Female patients of child-bearing potential must only be treated with oral isotretinoin if they are participating in the approved pregnancy prevention and management program (iPLEDGE). • Mood disorders, depression, suicidal ideation, and suicides have been reported in patients taking this drug. However, a causal

	relationship has not been established. **Recommendations** *Isotretinoin* Strength of recommendation = A. Level of evidence = I. References: Peck et al., 1982; Lehucher-Ceyrac & Weber-Buisset, 1993; Goulden et al., 1997; Strauss et al., "A randomized trial," 2001; McElwee et al., 1991; Strauss et al., "Safety," 2001; Dai, LaBraico, & Stern, 1992; Goldsmith et al., 2004; Rubinow et al., 1987
FMSD (2007)	**Local Treatment** • Comedonic acne can be treated with • Retinoic acid cream or solution (tretinoin [**A**], isotretinoin [**B**]) **Indications for Specialist Consultation** • If ordinary treatment fails, the dermatologist can consider isotretinoin. However, it has considerable teratogenicity. A program called iPLEDGE has been set up to make sure that pregnant women do not take isotretinoin and that women do not become pregnant while taking isotretinoin.
ICSI (2006)	**Clinical Highlights and Recommendations** • Isotretinoin therapy is highly regulated. *(Annotation #9 in the original guideline document)* **Oral Retinoids** Isotretinoin is the only oral retinoid approved for use in acne and is a well established teratogen. Although causality has not been determined for depression and suicide this is an ongoing concern. In view of these factors its use is highly regulated by the FDA. Only providers registered with the iPLEDGE program may prescribe Isotretinoin. For information about this program conduct an internet search using: iPLEDGE program. This program is scheduled to start March 1, 2006 and replaces the existing System to Manage Accutane Related Teratogenicity (S.M.A.R.T.) program.
Adjunctive Therapies	
AAD (2007)	**<u>Hormonal Agents</u>**

- Estrogen-containing oral contraceptives can be useful in the treatment of acne in some women.
- Oral antiandrogens, such as spironolactone and cyproterone acetate, can be useful in the treatment of acne. While flutamide can be effective, hepatic toxicity limits its use. There is no evidence to support the use of finasteride.
- There are limited data to support the effectiveness of oral corticosteroids in the treatment of acne. There is a consensus of expert opinion that oral corticosteroid therapy is of temporary benefit in patients who have severe inflammatory acne.
- In patients who have well-documented adrenal hyperandrogenism, low-dose oral corticosteroids may be useful in treatment of acne.

Recommendations

Contraceptive Agents

Strength of recommendation = A. Level of evidence = I. References: Lucky et al., 1997; Olson, Lippman, & Robisch, 1998; Thiboutot et al., 2001; Leyden et al., 2002

Spironolactone

Strength of recommendation = B. Level of evidence = II. References: Muhlemann et al., 1986

Antiandrogens

Strength of recommendation = B. Level of evidence = II. References: Greenwood et al., 1985; Miller et al., 1986

Oral Corticosteroids

Strength of recommendation = B. Level of evidence = II. References: Nader et al., 1984

Miscellaneous Therapy

- Intralesional corticosteroid injections are effective in the treatment of individual acne nodules.
- There is limited evidence regarding the benefit of physical modalities including glycolic acid peels and salicylic acid peels.

Recommendations

Intralesional Steroids

Strength of recommendation = C. Level of evidence = III. References:

Levine & Rasmussen, 1983; Potter, 1971

Chemical Peels

Strength of recommendation = C. Level of evidence = III. References: Kim et al., 1999; Wang et al., 1997; Grimes, 1999

Comedo Removal

Strength of recommendation = C. Level of evidence = III. References: Pepall, Cosgrove, & Cunliffe, 1991

Complementary Therapy

- Herbal and alternative therapies have been used to treat acne. Although these products appear to be well tolerated, very limited data exist regarding the safety and efficacy of these agents.

Recommendations

Herbal Agents

Strength of recommendation = B. Level of evidence = II. References: Bassett, Pannowitz, & Barnetson, 1990; Paranjpe & Kulkarni, 1995; Laala et al., 2001

Psychological Approaches

Strength of recommendation = C. Level of evidence = III. References: Ellerbroek, 1973

Hypnosis/Biofeedback

Strength of recommendation = B. Level of evidence = II. References: Hughes et al., 1983

Dietary Restriction

- Dietary restriction (either specific foods or food classes) has not been demonstrated to be of benefit in the treatment of acne.

Recommendation

Effect of Diet

Strength of recommendation = B. Level of evidence = II. References: Bett, Morland, & Yudkin, 1967; Fulton, Plewig, & Kligman, 1969

FMSD (2007)	**<u>Light Therapy, Cyst Injections, Hormonal Treatment</u>**
	
	Local Treatment
	
	• Common acne can be treated with
	  • Ultraviolet light therapy (as a course of 15 treatments added to other treatment) for widespread disease
	
	Systemic Treatment
	
	• Antibiotics
	  • Local treatment and light therapy can be used simultaneously with systemic treatment.
	  • Local treatment is not sufficient in cystic acne and conglobate acne. Use systemic antibiotics or consider referral to a dermatologist. Pus-containing cysts can be drained by incising them with a large-caliber injection needle or narrow-tipped scalpel.
	• Hormonal treatment for women
	  • Cyproterone acetate (an anti-androgen) + oestrogen for 6 months reduce the excretion of sebaceous glands and alleviate acne.

ICSI (2006)	**<u>Consider Adjunctive Therapy</u>** **Oral Contraceptives** The addition of combination oral contraceptives has been shown to be effective in the treatment of acne. *[Conclusion Grade I: See Conclusion Grading Worksheet C — Annotation #9 (Oral Contraceptives)] in the original guideline document* Treatment with a combined oral contraceptive (estrogen and progestin) is an alternative for women who fail conventional acne therapies. Oral contraceptives are effective for the treatment of acne due to their androgen modulating properties. It is the estrogen component of combined oral contraceptives that reduces androgen production and decreases the amount of free and active testosterone by increasing the production of sex hormone binding globulin. Progestin-only oral contraceptives are not effective and may worsen acne. Responses may not be seen for 3 to 6 months, with some patients showing a flare of symptoms during early cycles. Although some progestins have exhibited androgenic properties during in vitro and animal studies, all combination oral contraceptives have antiandrogenic properties due to the estrogen component. To ensure adherence with therapy, the ideal product is one that has the lowest incidence of adverse effects for a particular patient. Products with FDA indications for acne include Estrostep® and Ortho Tri-cyclen®.

	Spironolactone Spironolactone is a medication primarily used in the treatment of hypertension. Due to its antiandrogenic effect, it has occasionally been used to treat adult onset acne in women when other treatments have been ineffective. It is the effects of testosterone that are felt to be a contributing factor to the development of acne in adult females. The drug acts by blocking the effects of testosterone on the oil glands and hair follicles of the female patient The result is a reduction in oil production that may lead to improvement of their acne. The optimal dosage varies, but ranges from 50 mg to 200 mg daily. Response may take two to three months*. The drug should not be used in pregnancy. Women of child-bearing age should use birth control methods while taking the medication. Side effects are rare, usually related to menstrual irregularity, mild gastrointestinal (GI) upset, or headache. The medication may be taken for one to two years with periodic rest periods. * Spironolactone can cause decreased sodium and increased potassium. Levels should be initially measured and carefully monitored at appropriate intervals. **Intra-lesional Injections** There are rare circumstances in which you may consider injecting large acne cysts with a corticosteroid for short-term cosmetic improvement. Each injection carries a risk of causing skin atrophy. Repeated injections are not recommended. The concentration of Triamcinolone varies from 2 to 10 mg/cc. The stock 10-, 25- or 40- mg/mL steroid suspension should be diluted with lidocaine and only enough injected through a 1- mL syringe with a 27- or 30- gauge needle to distend the cyst slightly (usually 0.025 mL to 0.1 mL). **Light Therapy** There continue to be numerous studies about light treatment for acne, including blue light and photodynamic therapy with and without pretreatment with topical medications. At this time, the evidence is inadequate to make a recommendation about the efficacy and safety of these treatments.
Follow-Up	
AAD (2007)	No recommendations offered.
FMSD (2007)	**Indications for Specialist Consultation** • Severe forms of acne (A. cystica, conglobata, fulminans) • If ordinary treatment fails, the dermatologist can consider

	isotretinoin. However, it has considerable teratogenicity. **Acne Scars** • Consider treatment of scars by skin abrasion or laser therapy [**D**] only after the activity of the disease has totally subsided. • Scars can be treated either by a dermatologist or a plastic surgeon.
ICSI (2006)	**Clinical Highlights and Recommendations** • Patient perception of improvement is the best measure of successful treatment *(Annotation #4 in the original guideline document)* • The patient needs to understand that acne may get worse before it gets better. It typically takes eight weeks of treatment before a response is noted. *(Annotation #7 in the original guideline document)* **Follow-Up 6-12 Weeks/Satisfactory Response?** There is no clear evidence to support a specific duration of any treatment for acne. However, clinical experience and clinical trials suggest that a minimum treatment period of 6-12 weeks is needed before an improvement will be noted in most patients. **Assess Outcome and Adherence** Asking non-threatening, open-ended questions during patient interviews can be a useful method of assessing medication adherence. The interview should include probes for factors that contribute to non-adherence including adverse reactions, misunderstandings of asymptomatic or chronic disease treatment, depression, cognitive impairment, complex dosing regimens, and financial constraints. *Supporting evidence is of class: R* **Modify Treatment Plan** *Consider Different/Additional Medications* It may be necessary to switch to a different class of topical acne medication. For example: if the patient is on a benzoyl peroxide product or a combination product and is not responding, consider switching to a once daily topical retinoid, and a once daily topical anti-infective. For moderate to severe acne, consider adding an oral antibiotic or switching the current oral antibiotic. Selection is based on patient specific factors.

	Consider Dermatology Referral Dermatologists treat all forms of acne, particularly severe cases. For those patients with severe inflammatory acne that has not improved with previously described medications, a retinoid, isotretinoin (Accutane), may be considered. Dermatologists may be helpful to guide you at any point of the algorithm. *Supporting evidence is of classes: A, R* For most current information regarding Isotretinoin: http://www.fda.gov/cdec/drug/infopage/accutane/default.htm **Maintenance** If stable on current topicals, continue treatment indefinitely. If stable on topical and systemic antibiotics, after clearance is achieved for 1 to 3 months, consider tapering oral antibiotics and continue topicals indefinitely.

Selected Supporting References

Note from NGC: Bolded references are cited in more than one guideline. Refer to the original guideline documents for a complete listing of supporting references.

AAD (2007)	Bassett IB, Pannowitz DL, Barnetson RS. A comparative study of tea-tree oil versus benzoylperoxide in the treatment of acne. Med J Aust 1990;153:455-8. Becker LE, Bergstresser PR, Whiting DA, Clendenning WE, Dobson RL, Jordan WP, et al. Topical clindamycin therapy for acne vulgaris. A cooperative clinical study. Arch Dermatol 1981;117:482-5. Belknap BS. Treatment of acne with 5% benzoyl peroxide gel or 0.05% retinoic acid cream. Cutis 1979;23:856-9. Bernstein JE, Shalita AR. Topically applied erythromycin in inflammatory acne vulgaris. J Am Acad Dermatol 1980;2: 318-21. Bett DG, Morland J, Yudkin J. Sugar consumption in acne vulgaris and seborrhoeic dermatitis. Br Med J 1967;3: 153-5. Blaney DJ, Cook CH. Topical use of tetracycline in the treatment of acne: a double-blind study comparing topical and oral tetracycline therapy and placebo. Arch Dermatol 1976;112:971-3.

Chalker DK, Lesher JL Jr, Smith JG Jr, Klauda HC, Pochi PE, Jacoby WS, et al. Efficacy of topical isotretinoin 0.05% gel in acne vulgaris: results of a multicenter, doubleblind investigation. J Am Acad Dermatol 1987;17:251-4.

Chalker DK, Shalita A, Smith JG Jr, Swann RW. A double-blind study of the effectiveness of a 3% erythromycin and 5% benzoyl peroxide combination in the treatment of acne vulgaris. J Am Acad Dermatol 1983;9:933-6.

Christian GL, Krueger GG. Clindamycin vs placebo as adjunctive therapy in moderately severe acne. Arch Dermatol 1975; 111:997-1000.

Christiansen JV, Gadborg E, Ludvigsen K, Meier CH, Norholm A, Pedersen D, et al. Topical tretinoin, vitamin A acid (Airol) in acne vulgaris. A controlled clinical trial. Dermatologica 1974; 148:82-9.

Dai WS, LaBraico JM, Stern RS. Epidemiology of isotretinoin exposure during pregnancy. J Am Acad Dermatol 1992;26: 599-606.

Dobson RL, Belknap BS. Topical erythromycin solution in acne. Results of a multiclinic trial. J Am Acad Dermatol 1980;3:478-82.

Ellerbroek WC. Hypotheses toward a unified field theory of human behavior with clinical application to acne vulgaris. Perspect Biol Med 1973;16:240-62.

Fulton JE Jr, Plewig G, Kligman AM. Effect of chocolate on acne vulgaris. JAMA 1969;210:2071-4.

Gammon WR, Meyer C, Lantis S, Shenefelt P, Reizner G, Cripps DJ. Comparative efficacy of oral erythromycin versus oral tetracycline in the treatment of acne vulgaris. A doubleblind study. J Am Acad Dermatol 1986;14:183-6.

Goldsmith LA, Bolognia JL, Callen JP, Chen SC, Feldman SR, Lim HW, et al. American Academy of Dermatology Consensus Conference on the safe and optimal use of isotretinoin: summary and recommendations. J Am Acad Dermatol 2004;50:900-6. Erratum in J Am Acad Dermatol 2004;51:348.

Goulden V, Clark SM, McGeown C, Cunliffe WJ. Treatment of acne with intermittent isotretinoin. Br J Dermatol 1997;137: 106-8.

Gratton D, Raymond GP, Guertin-Larochelle S, Maddin SW, Leneck CM, Warner J, et al. Topical clindamycin versus systemic tetracycline in the treatment of acne. Results of a multiclinic trial. J Am Acad Dermatol 1982;7:50-3.

Greenwood R, Brummitt L, Burke B, Cunliffe WJ. Acne: double blind clinical and laboratory trial of tetracycline, oestrogencyproterone acetate, and combined treatment. Br Med J (Clin Res Ed) 1985;291:1231-5.

Grimes PE. The safety and efficacy of salicylic acid chemical peels in darker racial-ethnic groups. Dermatol Surg 1999;25: 18-22.

Hersle K. Trimethoprim-sulphamethoxazole in acne vulgaris. A double-blind study. Dermatologica 1972;145:187-91.

Hjorth N, Graupe K. Azelaic acid for the treatment of acne. A clinical comparison with oral tetracycline. Acta Derm Venereol Suppl (Stockh) 1989;143:45-8.

Hughes H, Brown BW, Lawlis GF, Fulton JE Jr. Treatment of acne vulgaris by biofeedback relaxation and cognitive imagery. J Psychosom Res 1983;27:185-91.

Jones EL, Crumley AF. Topical erythromycin vs blank vehicle in a multiclinic acne study. Arch Dermatol 1981;117:551-3. 54. Prince RA, Busch DA, Hepler CD, Feldick HG. Clinical trial of topical erythromycin in inflammatory acne. Drug Intell Clin Pharm 1981;15:372-6.

Kim SW, Moon SE, Kim JA, Eun HC. Glycolic acid versus Jessnerï¿½s solution: which is better for facial acne patients? A randomized prospective clinical trial of split-face model therapy. Dermatol Surg 1999;25:270-3.

Lalla JK, Nandedkar SY, Paranjape MH, Talreja NB. Clinical trials of ayurvedic formulations in the treatment of acne vulgaris. J Ethnopharmacol 2001;78:99-102.

Lehucher-Ceyrac D, Weber-Buisset MJ. Isotretinoin and acne in practice: a prospective analysis of 188 cases over 9 years. Dermatology 1993;186:123-8.

Lesher JL Jr, Chalker DK, Smith JG Jr, Guenther LC, Ellis CN, Voorhees JJ, et al. An evaluation of a 2% erythromycinointment in the topical therapy of acne vulgaris. J Am Acad Dermatol 1985;12:526-31.

Levine RM, Rasmussen JE. Intralesional corticosteroids in the treatment of nodulocystic acne. Arch Dermatol 1983;119: 480-1.

Leyden JJ, Shalita AR, Saatjian GD, Sefton J. Erythromycin 2% gel in comparison with clindamycin phosphate 1% solution in acne vulgaris. J Am Acad Dermatol 1987;16:822-7.

Leyden J, Shalita A, Hordinsky M, Swinyer L, Stanczyk FZ, Weber ME.

Efficacy of a low-dose oral contraceptive containing 20 microg of ethinyl estradiol and 100 microg of levonorgestrel for the treatment of moderate acne: A randomized, placebo-controlled trial. J Am Acad Dermatol 2002;47:399-409.

Lookingbill DP, Chalker DK, Lindholm JS, Katz HI, Kempers SE, Huerter CJ, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. J Am Acad Dermatol 1997;37:590-5.

Lucky AW, Cullen SI, Jarratt MT, Quigley JW. Comparative efficacy and safety of two 0.025% tretinoin gels: results from a multicenter double-blind, parallel study. J Am Acad Dermatol 1998;38:S17-23.

Lucky AW, Henderson TA, Olson WH, Robisch DM, Lebwohl M, Swinyer LJ. Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. J Am Acad Dermatol 1997;37:746-54.

McElwee NE, Schumacher MC, Johnson SC, Weir TW, Greene SL, Scotvold MJ, et al. An observational study of isotretinoin recipients treated for acne in a health maintenance organization. Arch Dermatol 1991;127:341-6.

Miller YW, Eady EA, Lacey RW, Cove JH, Joanes DN, Cunliffe WJ. Sequential antibiotic therapy for acne promotes the carriage of resistant staphylococci on the skin of contacts. J Antimicrob Chemother 1996;38:829-37.

Miller JA, Wojnarowska FT, Dowd PM, Ashton RE, O'Brien TJ, Griffiths WA, et al. Anti-androgen treatment in women with acne: a controlled trial. Br J Dermatol 1986;114:705-16.

Mills O Jr, Thornsberry C, Cardin CW, Smiles KA, Leyden JJ. Bacterial resistance and therapeutic outcome following three months of topical acne therapy with 2% erythromycin gel versus its vehicle. Acta Derm Venereol 2002; 82:260-5.

Mills OH Jr, Kligman AM, Pochi P, Comite H. Comparing 2.5%, 5%, and 10% benzoyl peroxide on inflammatory acne vulgaris. Int J Dermatol 1986;25:664-7.

Muhlemann MF, Carter GD, Cream JJ, Wise P. Oral spironolactone: an effective treatment for acne vulgaris in women. Br J Dermatol 1986;115:227-32.

Nader S, Rodriguez-Rigau LJ, Smith KD, Steinberger E. Acne and hyperandrogenism: impact of lowering androgen levels with

glucocorticoid treatment. J Am Acad Dermatol 1984; 11:256-9.

Olson WH, Lippman JS, Robisch DM. The duration of response to norgestimate and ethinyl estradiol in the treatment of acne vulgaris. Int J Fertil Womens Med 1998;43: 286-90.

Paranjpe P, Kulkarni PH. Comparative efficacy of four Ayurvedic formulations in the treatment of acne vulgaris: a double-blind randomised placebo-controlled clinical evaluation. J Ethnopharmacol 1995;49:127-32.

Peck GL, Olsen TG, Butkus D, Pandya M, Arnaud-Battandier J, Gross EG, et al. Isotretinoin versus placebo in the treatment of cystic acne. A randomized double-blind study. J Am Acad Dermatol 1982;6:735-45.

Pepall LM, Cosgrove MP, Cunliffe WJ. Ablation of whiteheads by cautery under topical anaesthesia. Br J Dermatol 1991;125: 256-9.

Pochi PE, Bagatell FK, Ellis CN, Stoughton RB, Whitmore CG, Saatjian GD, et al. Erythromycin 2 percent gel in the treatment of acne vulgaris. Cutis 1988;41:132-6.

Potter RA. Intralesional triamcinolone and adrenal suppression in acne vulgaris. J Invest Dermatol 1971;57: 364-70.

Prince RA, Busch DA, Hepler CD, Feldick HG. Clinical trial of topical erythromycin in inflammatory acne. Drug Intell Clin Pharm 1981;15:372-6.

Rubinow DR, Peck GL, Squillace KM, Gantt GG. Reduced anxiety and depression in cystic acne patients after successful treatment with oral isotretinoin. J Am Acad Dermatol 1987;17:25-32.

Schutte H, Cunliffe WJ, Forster RA. The short-term effects of benzoyl peroxide lotion on the resolution of inflamed acne lesions. Br J Dermatol 1982;106:91-4.

Shalita AR, Chalker DK, Griffith RF, Herbert AA, Hickman JG, Maloney JM, et al. Tazarotene gel is safe and effective in the treatment of acne vulgaris: a multicenter, double-blind, vehicle-controlled study. Cutis 1999;63:349-54.

Skidmore R, Kovach R, Walker C, Thomas J, Bradshaw M, Leyden J, et al. Effects of subantimicrobial-dose doxycycline in the treatment of moderate acne. Arch Dermatol 2003; 139:459-64.

Smith JG Jr, Chalker DK, Wehr RF. The effectiveness of topical and oral tetracycline for acne. South Med J 1976;69: 695-7.

Smith EB, Padilla RS, McCabe JM, Becker LE. Benzoyl peroxide lotion

	(20 percent) in acne. Cutis 1980;25:90-2. Stoughton RB, Cornell RC, Gange RW, Walter JF. Doubleblind comparison of topical 1 percent clindamycin phosphate (Cleocin T) and oral tetracycline 500 mg/day in the treatment of acne vulgaris. Cutis 1980;26:424-5, 429. Strauss JS, Leyden JJ, Lucky AW, Lookingbill DP, Drake LA, Hanifin JM, et al. A randomized trial of the efficacy of a new micronized formulation versus a standard formulation of isotretinoin in patients with severe recalcitrant nodular acne. J Am Acad Dermatol 2001;45:187-95. Strauss JS, Leyden JJ, Lucky AW, Lookingbill DP, Drake LA, Hanifin JM, et al. Safety of a new micronized formulation of isotretinoin in patients with severe recalcitrant nodular acne: A randomized trial comparing micronized isotretinoin with standard isotretinoin. J Am Acad Dermatol 2001;45: 196-207. **Thiboutot D, Archer DF, Lemay A, Washenik K, Roberts J, Harrison DD. A randomized, controlled trial of a low-dose contraceptive containing 20 microg of ethinyl estradiol and 100 microg of levonorgestrel for acne treatment. Fertil Steril 2001;76:461-8.** Tschen EH, Katz HI, Jones TM, Monroe EW, Kraus SJ, Connolly MA, et al. A combination benzoyl peroxide and clindamycin topical gel compared with benzoyl peroxide, clindamycin phosphate, and vehicle in the treatment of acne vulgaris. Cutis 2001;67:165-9. Wang CM, Huang CL, Hu CT, Chan HL. The effect of glycolic acid on the treatment of acne in Asian skin. Dermatol Surg 1997;23:23-9. Zouboulis CC, Derumeaux L, Decroix J, Maciejewska-Udziela B, Cambazard F, Stuhlert A. A multicentre, single-blind, randomized comparison of a fixed clindamycin phosphate/tretinoin gel formulation (Velac) applied once daily and a clindamycin lotion formulation (Dalacin T) applied twice daily in the topical treatment of acne vulgaris. Br J Dermatol 2000; 143:498-505.
FMSD (2007)	Farquhar C, Lee O, Toomath R, Jepson R. Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Cochrane Database Syst Rev 2003;(4):CD000194. Garner SE, Eady EA, Popescu C, Newton J, Li WA. Minocycline for acne vulgaris: efficacy and safety. Cochrane Database Syst Rev 2003;(1):CD002086. [143 references] PubMed Jordan R, Cummins C, Burls A. Laser resurfacing of the skin for the improvement of facial acne scarring. Birmingham: Department of Public Health and Epidemiology, University of Birmingham. West Midlands

	Development and Evaluation Service, Department of Public Health and Epidemiology (DPHE). DPHE Report No. 11. 1998. 1- 51p. Purdy S. What are the effects of topical treatments in people with acne vulgaris?. Clin Evid 2005;13:2042-59. The Health Technology Assessment Database, Database no: HTA-998502. In: The Cochrane Library [database online]. Issue 1. Oxford: Update Software; 2001
ICSI (2006)	Basler RS. Clindamycin for tetracycline-resistant acne. *Cutis* 1980;25:527-28. (Class D) Bershad S, Singer GK, Parente JE, et al. Successful treatment of acne vulgaris using a new method: results of a randomized vehicle-controlled trial of short-contact therapy with 0.1% tazarotene gel. *Arch Dermatol* 2002;138:481-89. (Class A) Bershad SV. The modern age of acne therapy: a review of current treatment options. *Mount Sinai J Med* 2001;68:279-86. (Class R) Bleeker J. Tolerance and efficacy of erythromycin stearate tablets versus enteric-coated erythromycin base capsules in the treatment of patients with acne vulgaris. *J Int Med Res* 1983;11:38-41. (Class A) Bleeker J, Hellgren L, Vincent J. Effect of systemic erytrhomycin stearate on the inflammatory lesions and skin surface fatty acids in acne vulgaris. *Dermatologica* 1981;162:342-49. (Class A) **Christian GL, Krueger GG. Clindamycin vs placebo as adjunctive therapy in moderately severe acne. Arch *Dermatol* 1975;111:997-1000. (Class C)** Doggrell SA, Brown L. The spironolactone renaissance. Expert *Opin Investig Drugs* 2001;10:943-54. (Class R) Drake LA, Ceilley RI, Cornelison RL, et al. Guidelines of care for acne vulgaris. *J Am Acad Dermatol* 1989;22:676-80. (Class R) **Gammon WR, Meyer C, Lantis S, et al. Comparative efficacy of oral erythromycin versus oral tetracycline in the treatment of acne vulgaris: a double-blind study. *J Am Acad Dermatol* 1986;14:183-86. (Class A)** Graupe K, Cunliffe WJ, Gollnick HP, Zaumseil RP. Efficacy and safety of topical azelaic acid (20 percent cream): an overview of results from European clinical trials and experimental reports. *Cutis* 1996;57:20-35. (Class R)

Harcup JW, Cooper J. The treatment of acne vulgaris in general practice. A double-blind assessment of co-trimoxazole and tetracycline. *Practitioner* 1980;224:747-50. (Class A)

Hersle K. Trimethoprim-sulfamethoxazole in acne vulgaris. A double-blind study. *Dermatologica* 1972;145:187-91. (Class C)

Hubbell CG, Hobbs ER, Rist T, White JW Jr. Efficacy of minocycline compared with tetracycline in treatment of acne vulgaris. *Arch Dermatol* 1982;118:989-92. (Class A)

Hughes BR, Norris JFB, Cunliffe WJ. A double-blind evaluation of topical isotretinoin 0.05%, benzoyl peroxide gel 5% and placebo in patients with acne. *Clin and Experimental Dermatol* 1992;17:165-68. (Class A)

Johnson BA, Nunley JR. Use of systemic agents in the treatment of acne vulgaris. *Am Fam Phys* 2000;15:1823-30, 35-36. (Class R)

Koulianos G. Treatment of acne with oral contraceptives: Criteria for pill selection. *Cutis* 2000;66:281-86. (Class R)

Lesher JL, Chalker DK, Smith JG, et al. An evaluation of a 2% erythromycin ointment in the topical therapy of acne vulgaris. *J Am Acad Dermatol* 1985;12:526-31. (Class A)

Leyden JJ. Current issues in antimicrobial therapy for the treatment of acne. *JEADV* 2001;15:51-55.(Class R)

Leyden JJ. Therapy of acne vulgaris. *N Engl J Med* 1997;336:1156-62. (Class R)

Lookingbill DP, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindamycin/ benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double-blind investigations. *Am Acad of Dermatol* 1997;37:590-95. (Class A)

Lucky AW, Cullen SI, Funicella T, et al. Double-blind, vehicle-controlled, multicenter comparison of two 0.025% tretinoin creams in patients with acne vulgaris. *J Am Acad Dermatol* 1998;38:S24-30. (Class A)

Lucky AW, Henderson TA, Olson WH, et al. Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. *J Am Acad Dermatol* 1997;37:746-54. (Class A)

Mancini AJ. Acne vulgaris: a treatment update. *Contemporary Pediatrics* 2000;12:122. (Class R)

Nichols-English G, Poirier S. Optimizing adherence to pharmaceutical

	care plans. *J Am Pharm Assoc* 2000;40:475-85. (Class R) Panzer JD, Poche W, Meek TJ, Derbes VJ, Atkinson W. Acne treatment: a comparative efficacy trial of clindamycin and tetracycline. *Cutis* 1977;19:109-11. (Class A) Redmond GP, Olson WH, Lippman JS, et al. Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: a randomized, placebo-controlled trial. *Obstet Gynecol* 1997;89:615-22. (Class A) Rosen MP, Breitkopf DM, Nagamani M. A randomized controlled trial of second- versus third-generation oral contraceptives in the treatment of acne vulgaris. *Am J Obstet Gynecol* 2003;188:1158-60. (Class A) Shalita A, Weiss JS, Chalker DK, et al. A comparison of the efficacy and safety of adapalene gel 0.1% and tretinoin gel 0.025% in the treatment of acne vulgaris: a multicenter trial. *J Am Acad Dermatol* 1996;34:482-85. (Class A) **Thiboutot D, Archer DF, Lemay A, et al. A randomized, controlled trial of a low-dose contraceptive containing 20 micrograms of ethinyl estradiol and 100 micrograms of levonorgestrel for acne treatment. *Fertility and Sterility* 2001;76:461-68. (Class A)** Webster GF. Acne Vulgaris. *BMJ* 2002;325:475-79. (Class R) Worret I, Arp W, Zahradnik HP, et al. Acne resolution rates: results of a single-blind, randomized, controlled, parallel phase III trial with EE/CMA (belara®) and EE/LNG (microgynon®). *Dermatology* 2001;203:38-44. (Class A)

TABLE 5: BENEFITS AND HARMS	
Benefits	
AAD (2007)	Appropriate management of acne vulgaris
FMSD (2007)	Effective treatment of acne
ICSI (2006)	Effective treatment of acne can decrease such negative effects of acne as decreased self-esteem, social withdrawal, anger, conduct disorders, and decreased employability. Patient perception of improvement is the best measure of successful treatment.

Harms	
AAD (2007)	**Topical Antibiotics** • The use of topical antibiotics alone can be associated with the development of bacterial resistance. **Oral Antibiotics** • A major problem affecting antibiotic therapy of acne has been bacterial resistance, which has been increasing. Resistance has been seen with all antibiotics, but is most common with erythromycin. • The use of oral antibiotics for the treatment of acne may be associated with adverse effects. Vaginal candidiasis may complicate the use of all oral antibiotics. Doxycycline can be associated with photosensitivity. Minocycline has been associated with pigment deposition in the skin, mucous membranes and teeth particularly among patients receiving long-term therapy and/or higher doses of the medication. Pigmentation occurs most often in acne scars, anterior shins, and mucous membranes. Autoimmune hepatitis, a systemic lupus erythematosus-like syndrome, and serum sickness-like reactions occur rarely with minocycline. **Hormonal Agents** • While flutamide can be effective, hepatic toxicity limits its use. • Spironolactone may cause hyperkalemia, particularly when higher doses are prescribed or when there is cardiac or renal compromise. It occasionally causes menstrual irregularity. **Isotretinoin** • Oral isotretinoin is a potent teratogen. • Side effects include those of the mucocutaneous, musculoskeletal, and ophthalmic systems, as well as headaches and central nervous system effects. Most of the adverse effects are temporary and resolve after the drug is discontinued. • While hyperostosis, premature epiphyseal closure, and bone demineralization have been observed with prolonged use of higher dose retinoids, in the usual course of acne treatment these findings have not been identified. Therefore it is the unanimous opinion of the acne work group that routine screening for these issues is not required. Laboratory monitoring during therapy should include triglycerides, cholesterol, transaminase, and complete blood counts. • Changes in mood, suicidal ideation, and suicide have been reported sporadically in patients taking isotretinoin. While these events have been seen, a causal relationship has not been established. Nonetheless, patients must be made aware of this possibility and

	treating physicians should monitor patients for psychiatric adverse effects. **Intralesional Steroids** • Systemic absorption of steroids may occur. Adrenal suppression was observed in one study. The injection of intralesional steroids may be associated with local atrophy.
FMSD (2007)	**Adverse Effects of Medication** • Retinoic acid cream or solution, adapalen gel, and benzoyl peroxide (3 to 10%) can be irritating at first. The tolerance of the skin increases with time. • Isotretinoin has considerable teratogenicity
ICSI (2006)	See the appropriate tables in the original guideline document for information on adverse effects of benzoyl peroxide, topical retinoids, azelaic acid, topical antibiotics, combination products, and first- and second-line oral antibiotics. **Spironolactone** • Side effects are rare, usually related to menstrual irregularity, mild gastrointestinal upset, or headache. Women of childbearing age should use birth control methods while taking the medication. • Spironolactone can cause decreased sodium and increased potassium. Levels should be initially measured and carefully monitored at appropriate intervals. **Oral Retinoids** • Isotretinoin is a well established teratogen. • Although causality has not been determined for depression and suicide this is an ongoing concern. • In view of these factors its use is highly regulated by the U.S. Food and Drug Administration (FDA). **Intra-lesional Injections** • Injections carry the risk of causing skin atrophy. • Repeated injections are not recommended.

TABLE 6: EVIDENCE RATING SCHEMES	
AAD (2007)	**Levels of Evidence** I. Good quality patient-oriented evidence II. Limited quality patient-oriented evidence III. Other evidence including consensus guidelines, extrapolations from bench research, opinion, or case studies **Strength of Recommendations** 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, or case studies.
FMSD (2007)	**Classification of the Quality of Evidence** A. **Quality of Evidence: High.** Further research is very unlikely to change our confidence in the estimate of effect. • Several high-quality studies with consistent results • In special cases: one large, high-quality multi-centre trial B. **Quality of Evidence: Moderate.** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. • One high-quality study • Several studies with some limitations C. **Quality of Evidence: Low.** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. • One or more studies with severe limitations D. **Quality of Evidence: Very Low.** Any estimate of effect is very uncertain. • Expert opinion

	• No direct research evidence • One or more studies with very severe limitations
ICSI (2006)	**Conclusion Grades:** **Grade I**: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power. **Grade II**: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most. **Grade III**: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed. **Grade Not Assignable**: There is no evidence available that directly supports or refutes the conclusion. **Study Quality Designations**: The quality of the primary research reports and systematic reviews are designated in the following ways on the conclusion grading worksheets: **Positive**: indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis. **Negative**: indicates that these issues (inclusion/exclusion, bias, generalizability, and data collection and analysis) have not been adequately addressed. **Neutral**: indicates that the report or review is neither exceptionally

strong nor exceptionally weak.

Not Applicable: indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

	• Medical opinion

GUIDELINE CONTENT COMPARISON

The American Academy of Dermatology (AAD), the Finnish Medical Society Duodecim (FMSD), and the Institute for Clinical Systems Improvement (ICSI) present recommendations for management of acne and provide explicit reasoning behind their judgments. All three organizations rank the level of evidence for each major recommendation.

The guidelines differ somewhat in scope. While AAD and FMSD address primarily management of acne, ICSI also provides assessment and patient education recommendations. These topics, however, are beyond the scope of this synthesis. The FMSD guideline updates its 2006 recommendations, and the ICSI guideline updates its 2003 recommendations.

Guideline Methodology

All three organizations performed searches of electronic databases; FMSD also performed hand-searches of published literature (primary and secondary sources). AAD and FMSD provide relevant information about the electronic databases searched, with AAD also specifying the dates searched. The AAD search was guided by nine clinical questions developed by the workgroup, which can be found in a separately-prepared, systematic evidence report (see the "Availability of Companion Documents" field in the NGC summary of this guideline).

With regard to the review of the evidence, ICSI presents its arguments and rationale, along with references to supporting evidence, in a format corresponding to algorithm annotations. AAD and FMSD present their arguments in the form of recommendation statements, also with accompanying references to supporting evidence. AAD also includes discussion of the basis for each recommendation statement. All three groups used rating schemes to weight the quality and the strength of the evidence, and therefore denote the quality of the supporting evidence with the corresponding recommendation/algorithm annotation. In terms of methods used to analyze the evidence, FMSD performed a systematic review, and AAD and ICSI performed a systematic review with evidence tables.

All three groups provide reference lists (180 references for AAD, 5 references for FMSD, 53 for ICSI). AAD and FMSD link the evidence directly to their recommendation statements, while ICSI links the evidence directly to associated algorithm annotations. For selected recommendations, ICSI also directs the reader to Conclusion Grading Worksheets, which provide a description of studies used to draw the particular conclusion.

AAD discloses potential conflicts of interest of its workgroup members. FMSD does not state any potential financial disclosures or conflicts of interests. ICSI states

that none of its work group members have any potential conflicts of interest to disclose.

Management of Acne: Comparison of Recommendations Between the FMSD and ICSI Guidelines	
Topical Treatments	
AAD (2007)	Recommends benzoyl peroxide, topical retinoids, and topical antibiotics. Notes that data from clinical trials indicate that azelaic acid is effective. Data for other topical therapies is limited.
FMSD (2007)	Recommends benzoyl peroxide, topical retinoids, and topical antibiotics
ICSI (2006)	Recommends benzoyl peroxide, topical retinoids, azelaic acid, and topical antibiotics
Oral Antibiotics	
AAD (2007)	Recommends doxycycline and minocycline as first-line therapies, stating that they are more effective than tetracycline. Erythromycin should be reserved for patients who cannot take tetracyclines. Trimethoprim-sulfamethoxazole and trimethoprim alone are also effective in instances where other antibiotics cannot be used.
FMSD (2007)	Cites erythromycin and tetracycline as appropriate oral antibiotics
ICSI (2006)	Cites erythromycin, tetracycline, doxycycline, and minocycline as appropriate first-line antibiotics and clindamycin and sulfamethoxazole/trimethoprim as appropriate second-line antibiotics
Oral Retinoids (isotretinoin)	
AAD (2007)	Recommends isotretinoin as appropriate for the treatment of severe recalcitrant nodular acne, or for lesser degrees of acne that are treatment-resistant or for the management of acne that is producing either physical or psychological scarring. Warns about its teratogenic properties, addresses iPLEDGE program.
FMSD (2007)	Cites isotretinoin as a possible therapy, but only in the case of ordinary treatment failure and warns about its teratogenetic properties.
ICSI (2006)	Cites isotretinoin as a possible therapy, but only in the case of ordinary treatment failure and warns about its teratogenetic properties. Adds that isotretinoin use is highly-regulated by the FDA and that only

	providers registered with the iPLEDGE program may prescribe it.
Adjunctive Therapies	
AAD (2007)	Recommends estrogen-containing oral contraceptives for selected women. Oral antiandrogens can be useful in the treatment of acne. Intralesional corticosteroid injections are effective in the treatment of individual acne nodules, There is limited data regarding herbal and alternative therapies.
FMSD (2007)	Recommends UV light therapy, cystic drainage, and cyproterone acetate with oestrogen as adjunctive treatments.
ICSI (2006)	Recommends combined oral contraceptives, corticosteroid injections, and spironolactone as adjunctive treatments.
Follow-Up	
AAD (2007)	No recommendations offered.
FMSD (2007)	Recommends referral to a dermatologist for severe/persistent acne, as well as treatment of acne scars by skin abrasion or laser therapy after the acne has subsided.
ICSI (2006)	Recommends referral to a dermatologist for severe/persistent acne. Also addresses a 6 to 12 week follow-up, medication adherence questionnaires, and maintenance/modification of the treatment plan.

Areas of Agreement

Topical Treatments

All three groups are in general agreement regarding appropriate topical treatments, with all recommending benzoyl peroxide, topical retinoids, and topical antibiotics, or a combination of these products. The topical retinoids adapalene and tretinoin are recommended by FMSD and ICSI, with ICSI also recommending tazarotene. AAD states that there is no consensus about the relative efficacy of currently available topical retinoids (tretinoin, adapalane, tazarotene, and isotretinoin). While clindamycin is the only topical antibiotic addressed by FMSD, ICSI also cites erythromycin, sulfacetamide and several combination products comprised partly of antibiotics. AAD recommends erythromycin and clindamycin. In addition to the therapies addressed above, AAD and ICSI also recommend azelaic acid as a possible topical treatment option. AAD also states that salicylic acid is moderately effective in the treatment of acne.

Oral Antibiotics

Therapies recommended by both FMSD and ICSI include erythromycin and tetracycline. Other first-line oral antibiotics recommended by ICSI included doxycycline and minocycline. AAD similarly recommends doxycycline and minocycline as first-line therapies, stating that they are more effective than tetracycline. AAD, however, adds that erythromycin should be reserved for patients who cannot take tetracyclines. Trimethoprim-sulfamethoxazole and trimethoprim alone are also cited as effective by AAD in instances where other antibiotics cannot be used. Second-line therapies also cited by ICSI are clindamycin and sulfamethoxadole. ICSI adds there is not enough evidence to make recommendations regarding the use of azithromycin. All three groups are in agreement that oral antibiotics used concurrently with a topical treatment may be an effective treatment option.

Oral Retinoids (isotretinoin)

The three guidelines agree that isotretinoin is a possible therapy, but only in the case of ordinary treatment failure, with all three groups also strongly emphasizing its teratogenic properties. All three groups address the pregnancy prevention and management program, iPLEDGE.

Adjunctive Therapies

AAD and ICSI note that intralesional injection with corticosteroids may be appropriate, but warn that each injection carries a risk of causing skin atrophy. FMSD similarly notes that pus-containing cysts can be drained by incising them with a large-caliber injection needle or narrow-tipped scalpel. All three guidelines recommend therapies with anti-androgenic properties, but differ in the specific treatments recommended (see Areas of Differences below).

Follow-Up

FMSD and ICSI are in agreement that referral to a dermatologist is appropriate for severe and/or persistent acne that does not respond to other treatments, and that isotretinoin may be indicated for those patients.

Areas of Differences

Adjunctive Therapies

The guidelines offer different recommendations concerning certain adjunctive therapies, most notably regarding light therapy. While FMSD recommends ultraviolet light therapy combined with other treatments to treat common acne, ICSI states that the evidence is currently inadequate to make a recommendation regarding the efficacy and safety of light treatments. AAD does not address light therapy. All three groups recommend the use of anti-androgenic therapies, yet differ slightly in terms of the specific treatments they recommend. FMSD recommends cyproterone acetate combined with an oestrogen, while AAD and ICSI recommend combined oral contraceptives. AAD adds, however, that cyproterone acetate may be useful in the treatment of acne. AAD and ICSI also cite spironolactone as an appropriate treatment for its antiandrogenic properties,

with AAD noting that it may cause hyperkalemia. FMSD does not address this medication.

Follow-Up

ICSI goes into follow-up measures at greater length than FMSD, discussing a 6 to 12 week follow-up evaluation, medication adherence questionnaires, and maintenance/modification of the treatment plan. FMSD recommends treatment of acne scars by a dermatologist or plastic surgeon using skin abrasion or laser therapy after the acne has subsided; ICSI does not address scar removal. AAD does not address follow-up.

Conclusion

The guidelines are in general agreement that topical treatments and oral antibiotics are appropriate first-line treatments for acne, and that isotretinoin may be appropriate in the case of ordinary treatment failure. Recommendations differ regarding the use of certain adjunctive treatments, such as ultraviolet light therapy and anti-androgenic therapies.

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