ACNE VULGARIS UPDATE

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M.D

5 QUESTIONS

1-Acute or chronic ?
2-Diet& acne ?
3-Antibiotic resistance ?
4-Isotretinoin ?
5- Hormonal treatment ?

ACUTE OR CHRONIC ?

Characteristics of acne that define chronic diseases:

I. Recurrence or relapse

II. Prolonged course

III. Manifestation acute outbreaks , slow onset

IV. Psychological and social impact

Diet&Acne ?

FROM THE ACADEMY

Guidelines of care for the management of acne vulgaris

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Acne is one of the most common disorders treated by dermatologists and other health care providers. While it most often affects adolescents, it is not uncommon in adults and can also be seen in children. This evidence-based guideline addresses important clinical questions that arise in its management. Issues from grading of acne to the topical and systemic management of the disease are reviewed. Suggestions on use are provided based on available evidence. (J Am Acad Dermatol 2016;74:945-73.)

Key words: acne; acne management; acne vulgaris; amoxicillin; antiandrogens; azithromycin; benzoyl peroxide; clindamycin; contraceptive agents; diet and acne; doxycycline; erythromycin; grading and classification of acne; guidelines; hormonal therapy; isotretinoin; light therapies; microbiological and endocrine testing; oral corticosteroids; *Propionibacterium acnes*; retinoids; salicylic; spironolactone; systemic therapies; tetracyclines; topical antibiotics; trimethoprim.

Approaches to limit systemic antibiotic use in acne: Systemic alternatives, emerging topical therapies, dietary modification, and laser and light-based treatments

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Acne is one of the most common diseases worldwide and affects ~50 million individuals in the United States. Oral antibiotics are the most common systemic agent prescribed for the treatment of acne. However, their use might be associated with a variety of adverse outcomes including bacterial resistance and disruption of the microbiome. As a result, multiple treatment guidelines call for limiting the use of oral antibiotics in the treatment of acne, although actual prescribing often does not follow these guidelines. In this review, the rationale for concerns regarding the use of oral antibiotics for the management of acne is reviewed. In addition, we will discuss our approach to complying with the intent of the guidelines, with a focus on novel topical agents, dietary modification, laser and light-based modalities, and systemic medications, such as spironolactone, combined oral contraceptives, and oral isotretinoin. (J Am Acad Dermatol 2019;80:538-49.)

Table XII. Recommendations for the role of diet in acne

Given the current data, no specific dietary changes are recommended in the management of acne
Emerging data suggest that high glycemic index diets may be associated with acne
Limited evidence suggests that some dairy, particularly skim milk, may influence acne

Diet&acne ?

High glycemic load diets

Skim milk

Pure chocolate

Omega-3 fatty acids

Fish consumption

AAD (2019)

- Because high glycemic load diets (HGLDs) might increase levels of **insulin-like growth factor 1 (IGF1)** activity and activation, thereby inducing proliferation of both keratinocytes and sebocytes as well as simulating androgen production, some have proposed that **HGLDs might be pathogenic in acne**

- **We feel the practitioner should consider recommending LGLDs as a helpful adjuvant for the treatment of acne.**

IGF-1

- IGF-1 stimulates synthesis of androgens in both ovarian and testicular tissues and inhibits hepatic synthesis of sex hormone-binding globulin (SHBG) resulting in increased bioavailability of androgens. Both IGF- and androgens increase sebum production, which is implicated in acne.

Diet&acne

- Milk also increases comedogenicity through interactions with the IGF-1 pathway. Milk, particularly skim milk, is positively correlated with higher plasma IGF-1 levels.
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Diet&acne

- They also postulated that **skim** milk is more acnegenic because, in comparison with whole milk, skim milk contains **less estrogen**, a hormone known to reduce acne.
- No association with cheese or yogurt.

AAD (2019)

Whey protein constitutes 20% of protein in cow's milk, its insulin-promoting component could help to explain the possible link between milk and acne

Diet&acne

- Exacerbation of facial acne vulgaris after consuming **pure chocolat**. Conclusion: Four and 7 days after the one-time consumption of 100% chocolate, subjects with a history of acne vulgaris experienced worsening of their acne as measured by an increase in the number of acneiform lesions. The dose dependent relationship between the amount of chocolate consumed and the number of acneiform lesions on both days 4 and 7 and further supports the likelihood that the exacerbation of acne was related to the consumption of chocolate.

TREATMENT AND MANAGEMENT OF ACNE

TREATMENT AND MANAGEMENT OF ACNE

Early, Appropriate Treatment Best to Minimize Potential for Acne Scars

- Two key modifiable factors are linked to acne scars: a time delay between onset of acne and effective treatment and the extent/duration of inflammation.
- Early appropriate treatment that is continued for as long as necessary is the best way to prevent acne scarring.

Early, Appropriate Treatment Best to Minimize Potential for Acne Scars

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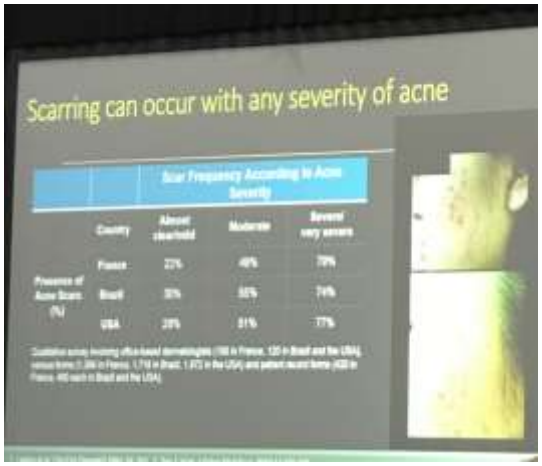
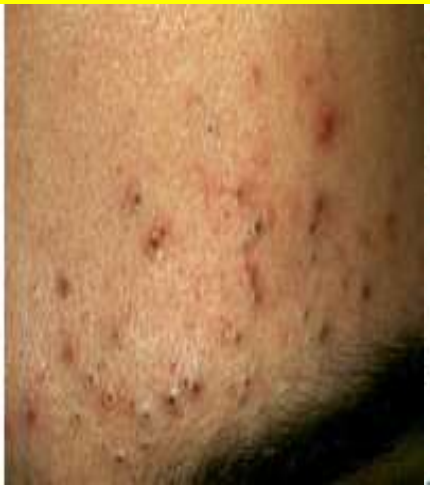
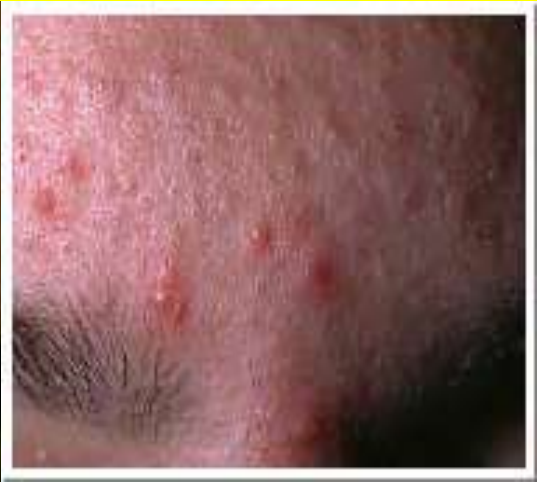


The 2016 European Acne

- **Guideline has used the following 4-point**
- 1) comedonal acne,
- 2) mild-moderate papulopustular acne;
- 3) severe papulopustular acne, moderate nodular acne;
- 4) severe nodular acne, conglobate acne.

Comedonal Acne





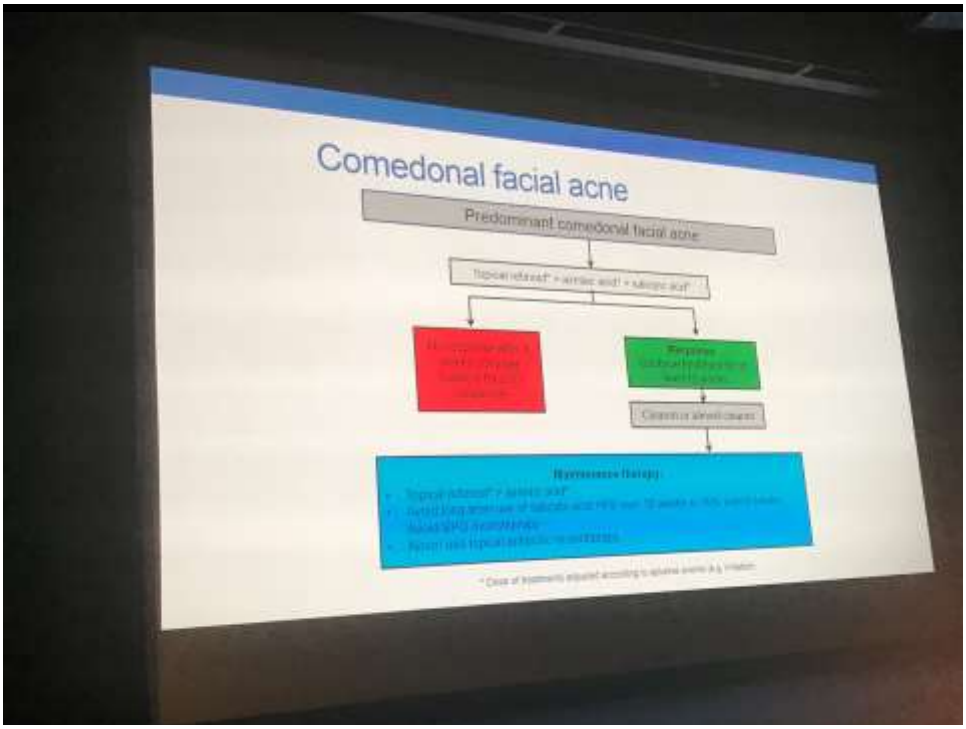


Table II. Strategies to minimize the likelihood of tolerability problems associated with induction of topical retinoid therapy

- Take a detailed patient history
  - Have there been tolerability problems in the past?
- Educate patient
  - Mild irritation can be part of the treatment process, but usually subsides within 1-2 weeks and can be managed with appropriate steps
  - A small dose of retinoid (demonstrate fingertip or pea-sized dose) should be applied in a thin layer to the entire affected area
  - Patient should use a gentle cleansing regimen and avoid overcleansing
- Select most tolerable retinoid formulation for climate and season
  - Creams and lotions might be best for dry or sensitive skin and gels or foam for more oily skin (although newer aqueous gels might also be suitable for sensitive skin)
- Titrate retinoid dose at initiation
  - Apply retinoid every other day for first 2-4 weeks (based on clinical trial evidence that this is when irritation is most likely to occur)
  - Apply gentle, noncomedogenic moisturizer
  - Use a short contact method for first 2-4 weeks (apply retinoid to full face for 30-60 minutes then wash off)

Adapted with permission from Leyden et al.[52]

Other topical agents

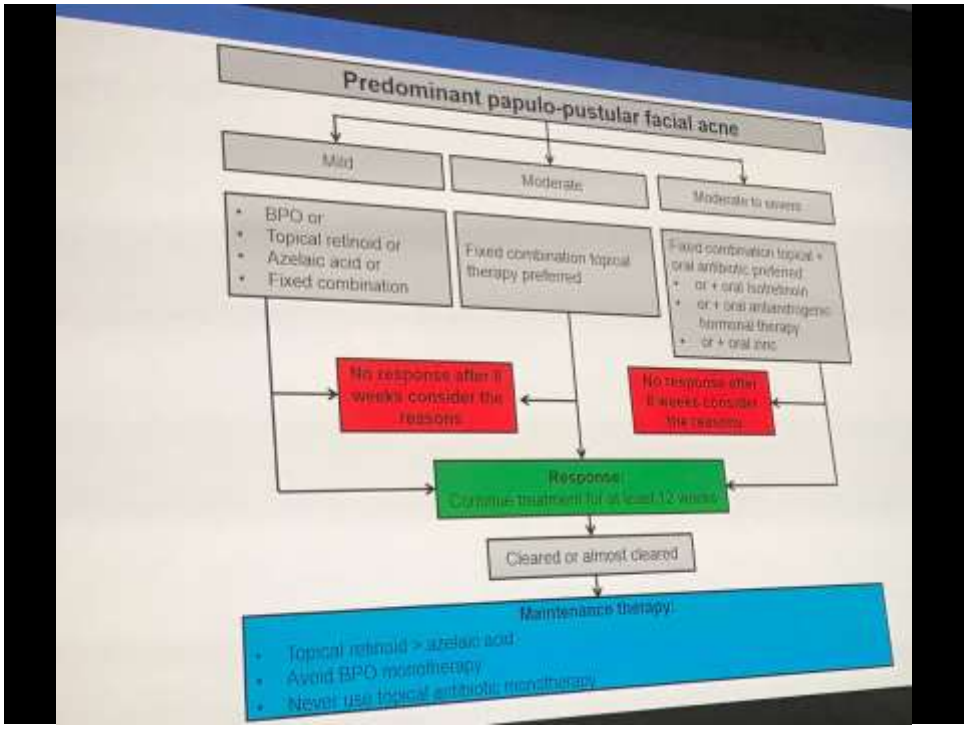
- **Azelaic acid 20%** has been reported to possess comedolytic and antibacterial properties. Data from clinical trials indicate that it is effective
- **Salicylic acid .**It often is used when patients cannot tolerate a topical retinoid because of skin irritation.
- DAPSONE GEL 5% IS AN EFFECTIVE, SAFE, NOVEL TOPICAL TREATMENT OF ACNE VULGARIS

Consider reasons for no response

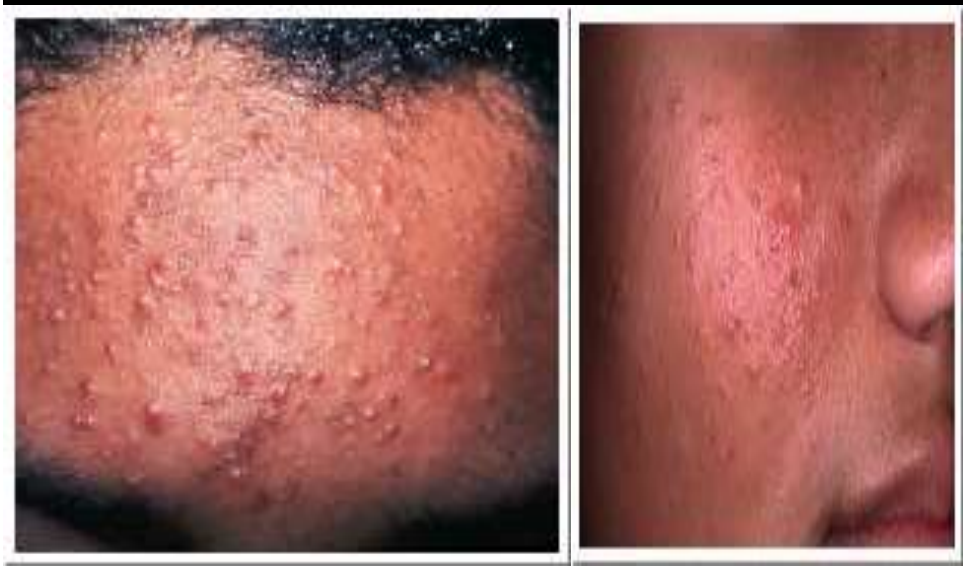
- Non drug related reasons
  - Seborrhoea
  - Acne provoking agents including cosmetics
  - Lifestyle factors
- Drug related reasons
  - Not working
  - Skin type
    - May need to adapt vehicle, consider skin care
  - Incorrect use of treatment
  - Drug related acne – hormones in females
- Poor adherence
- Adverse effects
- Progression of acne

	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 components. *BP,* Benzoyl peroxide.



Mild papulopustular acne



Benzoyl peroxide

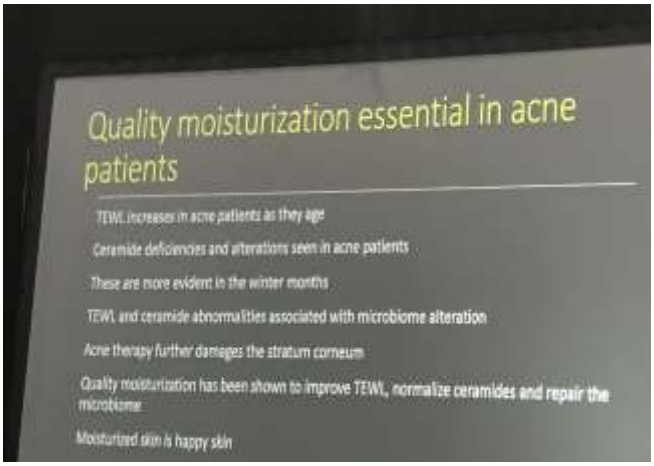
- Benzoyl peroxide (5%,10%) is a bactericidal agent that has proven effective in the treatment of acne.
- **Benzoyl peroxide 5%, is equal to 100 mg doxycycline.**

Topical antibiotics

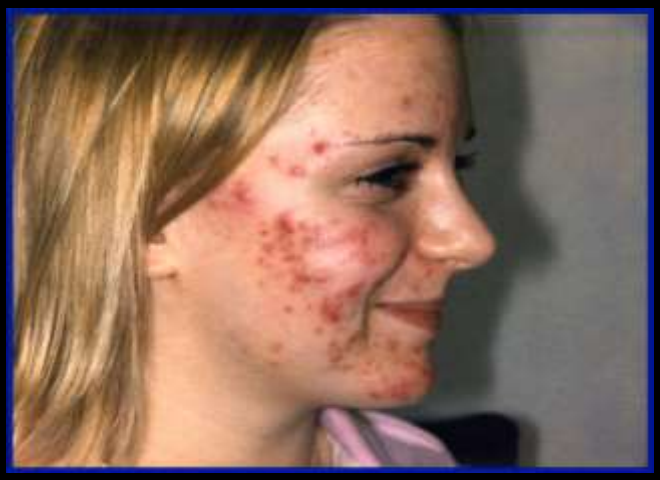
- Clindamycin 1%
- Erythromycin 2% and 4% with zinc acetate 1.2% .
- **Topical antibiotics** should be used in combination **with Retinoids** to prevent **antibiotic resistance**

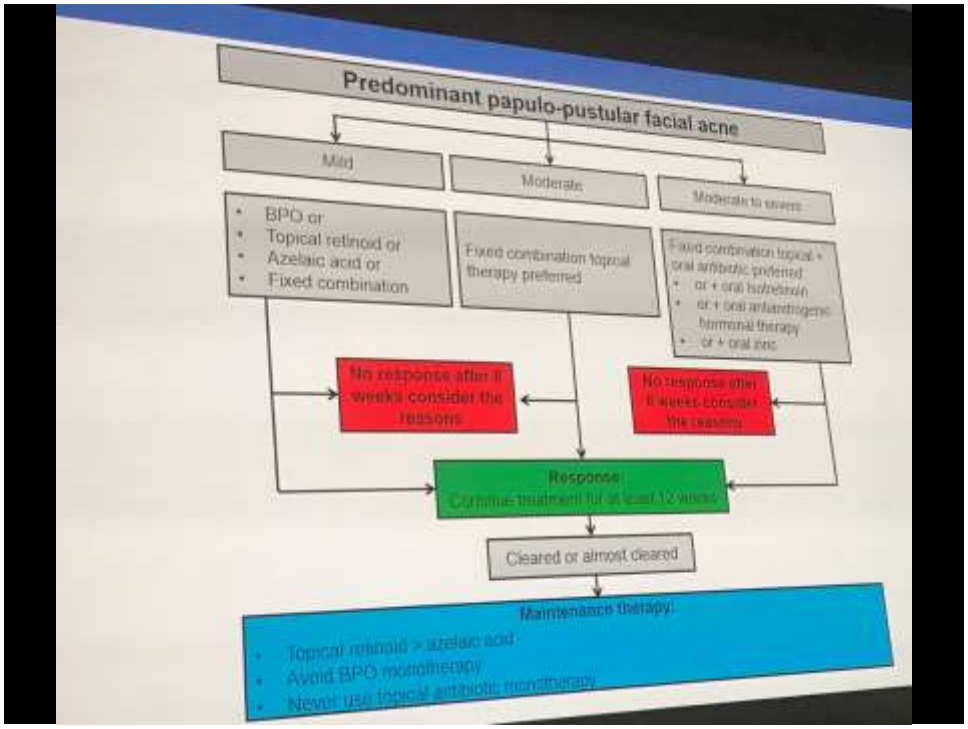

AMERICAN ACADEMY OF DERMATOLOGY
AAD
1938
2018 Annual Meeting


Barrier repair and microbiome
preservation/restoration in acne



Moderate Acne





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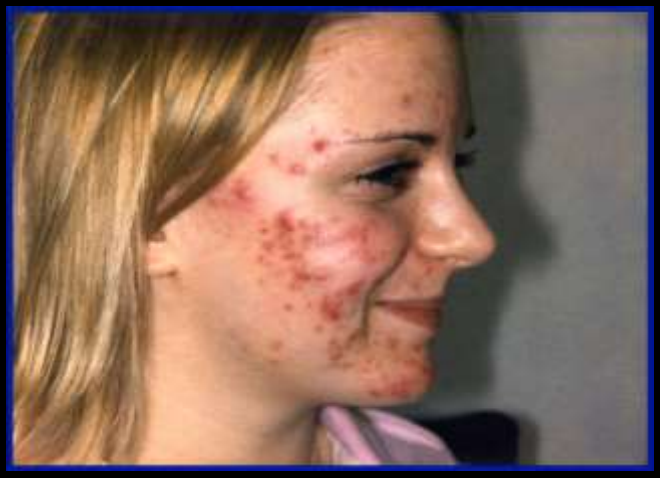
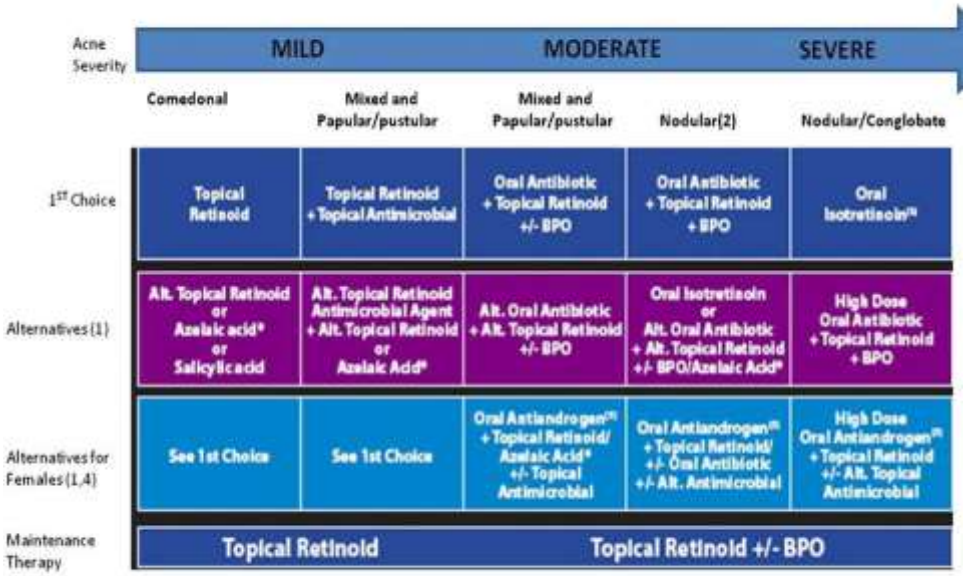


Global Alliance Acne Treatment Algorithm



1. Consider physical removal of comedones. 2. With small nodules (<0.5 cm). 3. Second course in case of relapse. 4. For pregnancy, options are limited. 5. For full discussion, see Gollnick H, et al. JAAD. 2003.49 (Suppl):1-37.

Oral antibiotics

- Tetracycline 1gm daily, doxycycline 100mg,
- Erythromycin 1gm, minocycline,
- Trimethoprim is increasingly used by dermatologists
- Clindamycin 150mg,3 times daily

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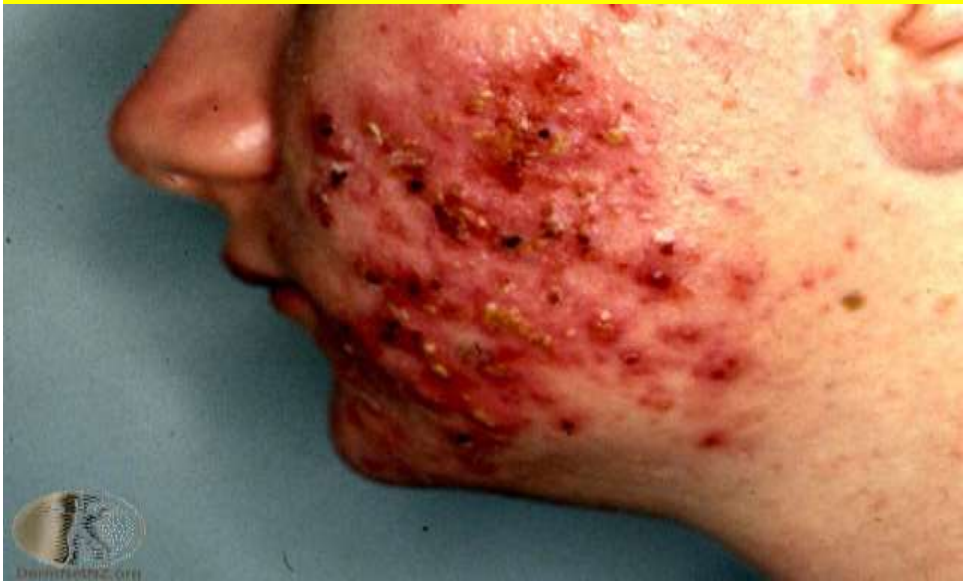
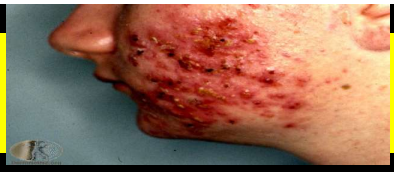
Strategies to Limit Antibiotic Resistance

- **Avoid using antibiotics (either oral or topical) as monotherapy.**
- **Avoid the simultaneous use of oral and topical antibiotics without BPO, particularly if chemically different.**



Gram-negative folliculitis

- Gram-negative folliculitis is an acne-like disorder caused by a bacterial infection. Gram-negative bacteria include *Escherichia coli*, *Pseudomonas aeruginosa*,*Serratimarcescens*, *Klebsiella* and *Proteus* species.
- The term "Gram negative" refers to the staining pattern of the organisms in the laboratory. Certain bacteria do not take up a stain known as "Gram".
- Gram-negative folliculitis may result from long-term treatment of acne with tetracycline or topical antibiotics.



- Gram-negative folliculitis is a pustular rash resembling acne. It is often mistaken as a worsening of acne as it usually occurs in patients with existing acne.
- In about 80% of patients, Gram-negative folliculitis causes **superficial pustules** with relatively few papules and comedones. These lesions are usually caused by ***Klebsiella*, *Escherichia* and *Serratia* species**.
- In about 20% of patients with Gram-negative folliculitis, lesions are **deep, nodular and cyst-like**. These are caused by *Proteus* species, which are able to invade deeply into the skin and create pus-filled abscesses and cysts.
- Gram-negative folliculitis lesions are usually found around the area of the upper lip, under the nose, to the chin and cheeks.

Treatment of acne during pregnancy

Topical benzoyl peroxide and topical erythromycin can be prescribed as individual therapies.

Azaleic acid is not prohibited during pregnancy.

Topical retinoids are not recommended for use in pregnant patients. However, pharmacologic data suggest that percutaneous absorption of such topical acne therapies is minimal.

Treatment of acne during pregnancy

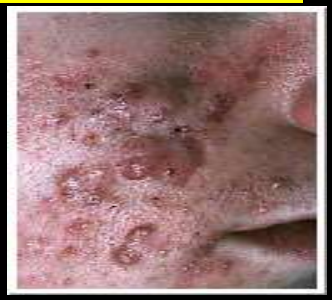
Topical benzoyl peroxide

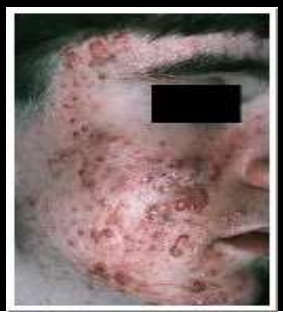
Topical erythromycin

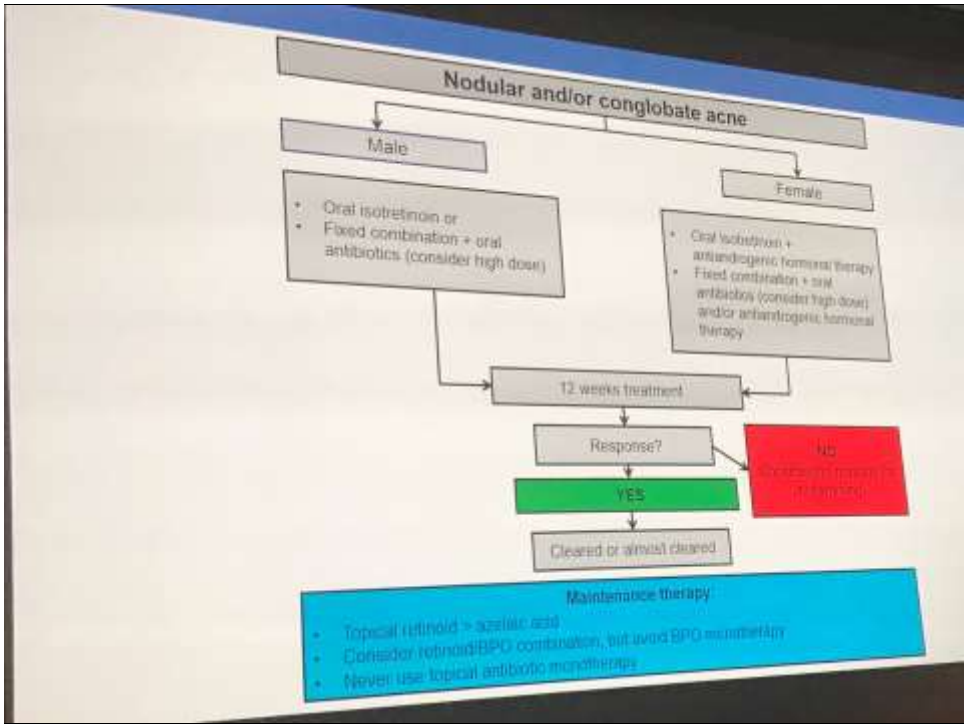
Azaleic acid

Topical retinoids.

Sever Acne

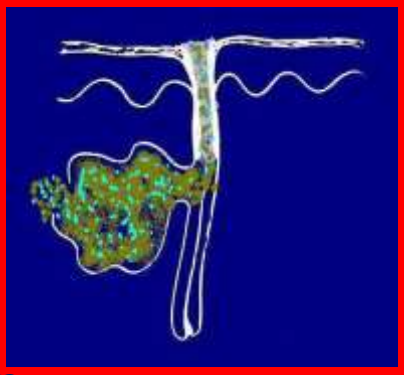






Pathogenesis of an acne lesion

- 1. Seborrhoea
- *2. Obstruction*
- *3. P. Acnes*
- *4. Inflammation*



Prognostic factors for early use of oral Isotretnoin

- Family history
- Early onset
- Persistent and late onset
- Hyperseborrhea
- Site of acne (chest&back)
- Psychological disability
- scarring

ISOTRETINOIN

- **0.5 to 1.0 mg/kg/day**, 20-week course.
- Back,trunk and buttocks may need 2 mg/kg/day .
- Cumulative dose of **120 to 150 mg/kg.**
- Pre-treatment with oral prednisone (0.5-1.0 mg/kg/day for 2-6 weeks, usually before initiation of isotretinoin.

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- **Low-dose isotretinoin (eg, 0.2-0.4 mg/kg/d)** has been demonstrated to have similar effectiveness and reduced side effects
- **Continuing treatment for at least 2 months after achieving no evidence of activity results in a decreased frequency of relapse.**

ISOTRETINOIN

Pulse therapy 0.5 mg/kg/day for 1 week each month for 6 months in mild to moderate acne.

First few weeks exacerbate.

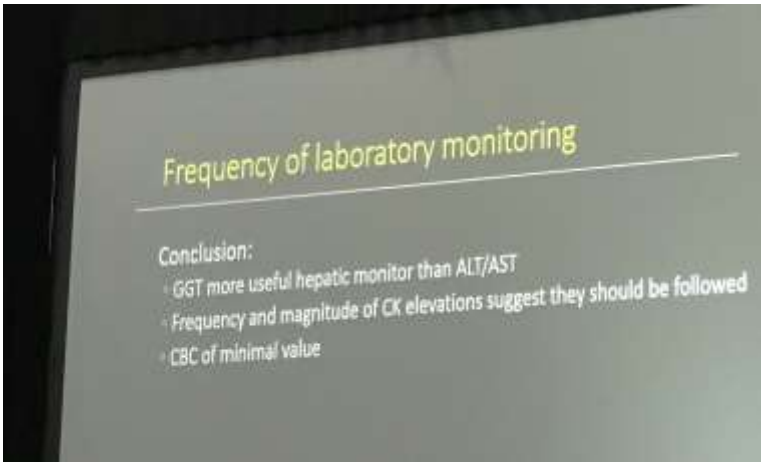
Improvement occur starting from week 8.

isotretinoin

- **An initial response is generally evident by week 8, and improvement continues through the end of a typical 20-week administration**.

ISOTRETINOIN

- should also be advised to take oral isotretinoin with food. As much as 40% of oral isotretinoin is absorbed when the drug is taken with food, whereas only about 20% is absorbed on an empty stomach



Standardized laboratory monitoring with use of isotretinoin in acne

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Background: Laboratory monitoring for adverse effects to isotretinoin occurs with variability. Standardization of laboratory monitoring practices represents an opportunity to improve quality of care.

Objective: We sought to develop an evidence-based approach to laboratory monitoring of patients receiving isotretinoin therapy for acne.

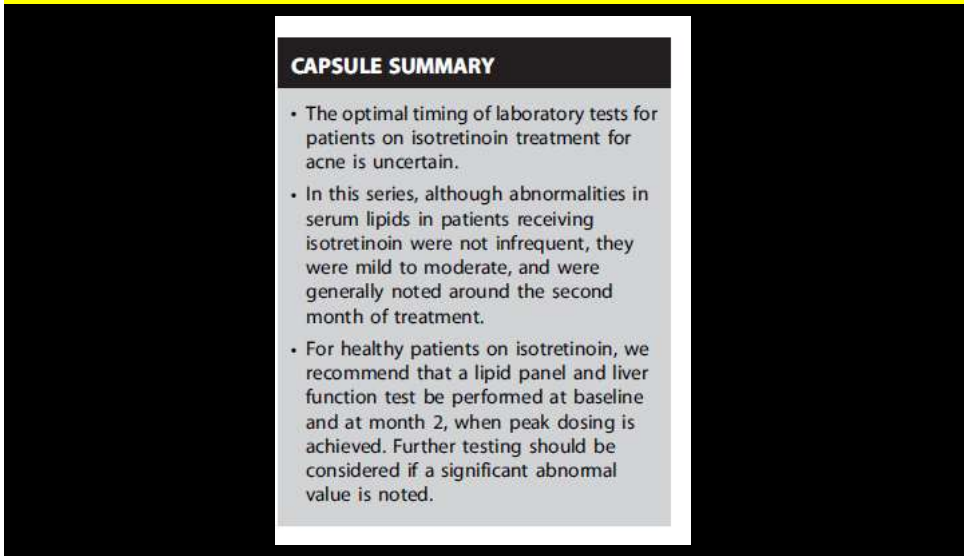
Methods: We reviewed laboratory data from 515 patients with acne undergoing 574 courses of isotretinoin from March 2003 to July 2011. Frequency, timing, and severity of abnormalities were determined.

Results: Clinically insignificant leukopenia or thrombocytopenia occurred in 1.4% and 0.9% of patients, respectively. Elevated liver transaminases were detected infrequently and not significantly increased compared with baseline detection rates (1.9% vs 1.6% at baseline). Significant elevations occurred with triglyceride (59.3%) and cholesterol (22.8%) levels. The most severe abnormalities were grade 2 (moderate). Mean duration of treatment before abnormalities were detected was 56.3 days for hypertriglyceridemia, 61.9 days for alanine transaminitis, and 90.1 days for hypercholesterolemia.

Limitations: This was a single-center experience examining variable isotretinoin laboratory monitoring practices.

Conclusions: In healthy patients with normal baseline lipid panel and liver function test results, repeated studies should be performed after 2 months of isotretinoin therapy. If findings are normal, no further testing may be required. Routine complete blood cell count monitoring is not recommended. (J Am Acad Dermatol 2016;75:323-8.)

Key words: acne; hypercholesterolemia; hypertriglyceridemia; isotretinoin; laboratory monitoring; leukopenia; thrombocytopenia; transaminitis.



Adverse events

- Dry, chapped lips and dry skin and eyes.
- Secondary skin infection with *S aureus*
- Muscle aches and backaches,
- Mild headaches
- Nosebleeds and skin fragility may also occur.
- Significant mood changes, depression

AAD(2019)

- **Myalgias can be reported in up to a quarter of patients receiving high-dose isotretinoin.**
- Importantly, these myalgias are **not** associated with **decreases in muscle strength or performance**

AAD(2019)

- Younger age at initial treatment and male sex are associated with an increased risk for relapse,
- **1 g/d omega-3 reduces muco-cutaneous side effects from isotretinoin**

AAD(2019)

- The relationship between **depression** and the use of isotretinoin is **uncertain.**
- Although isotretinoin is associated with **improved mood for the majority of patients** as their acne improves, it is sensible to educate the patient and family about depression and to monitor for concerning symptoms during treatment.

Optimizing therapy with oral retinoids

- **Avoiding hot showers and drying soaps,**
- **Moisturizers**
- **Contacts lens may need to switch to soft lenses or eyeglasses**

Adverse events

- Teratogenicity exists only while the retinoid is in the body; after the retinoid is cleared (typically 4 weeks after discontinuation of isotretinoin) there is no longer a risk.

Adverse events

- Severe headache, decreased night vision, or signs of adverse psychiatric events. (B.I.H)
- **Avoid concurrent Tetracycline.**

Adverse events

Acne flare(pseudopyogenic granuloma).

Accentuation of aleardy found lesions or marked pustulation.

Potent steroid ointement,cautery,15mg steroid with iso.

Oral corticosteroids

- If the patient has severe inflammatory lesions, acne fulminans, or pyoderma faciale, oral prednisone (0.5-1.0 mg/kg/day for 2-6 weeks, usually before initiation of isotretinoin) may be necessary. Topical keratolytics and drying agents should be avoided because isotretinoin has a drying effect on mucocutaneous tissues.

ISOTRETINOIN

- **Chemical peels or manual dermabrasion**.
- **laser hair removal, pulsed dye laser, and CO2.**

Recurrence

- **30% of patients relapsed**.
- low-dose isotretinoin therapy
- Severe acne,
- A prolonged history of acne,
- A female older than 25 at the onset of therapy.
- Truncal acne.

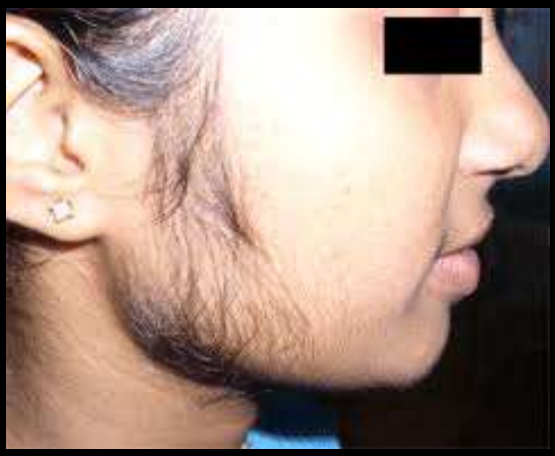
Recurrence

- less severe
- The recommendation is to wait at least 8 weeks

Hormonal influence

- **Adult or late onset**
- **Premenstrual flare**
- **Lower face, jaw lines, and chin.**
- **Excessive facial oilness**
- **Co excistance hirsutism or male pattern alopecia.**
- **Relapse shortly after isotretinoin therapy**
- **Hereditary factors**
- **Two external factors , stress, cosmetics**

Hirsutism



Hormonal influence

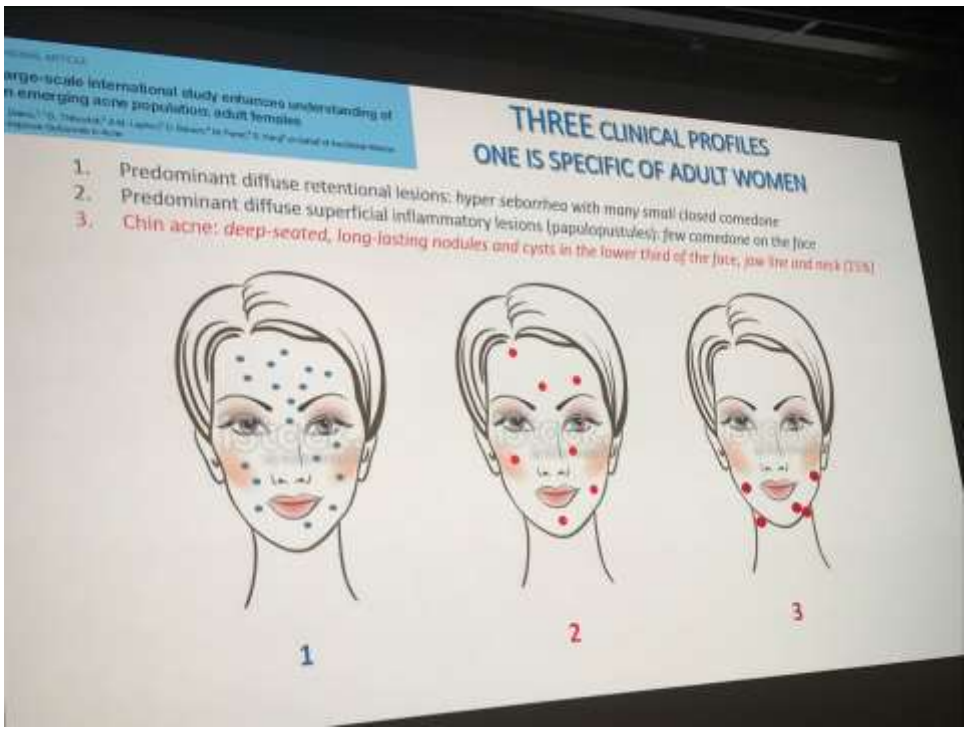
- Routine endocrinologic evaluation (eg, for androgen excess) is not indicated for the majority of patients with acne.
- Laboratory evaluation is indicated for patients who have acne and additional signs of androgen excess. In young children this may be manifested by body odor, axillary or pubic hair, and clitoromegaly. Adult women with symptoms of hyperandrogenism may present with recalcitrant or late-onset acne, infrequent menses, hirsutism, male or female pattern alopecia, infertility,acanthosis nigricans, and truncal obesity.

Hormonal influence

Screening tests for hyperandrogenism include serum DHEAS, total testosterone, free testosterone, luteinizing hormone/follicle stimulating hormone (LH/FSH) ratio, prolactin, and 17-hydroxyprogesterone.

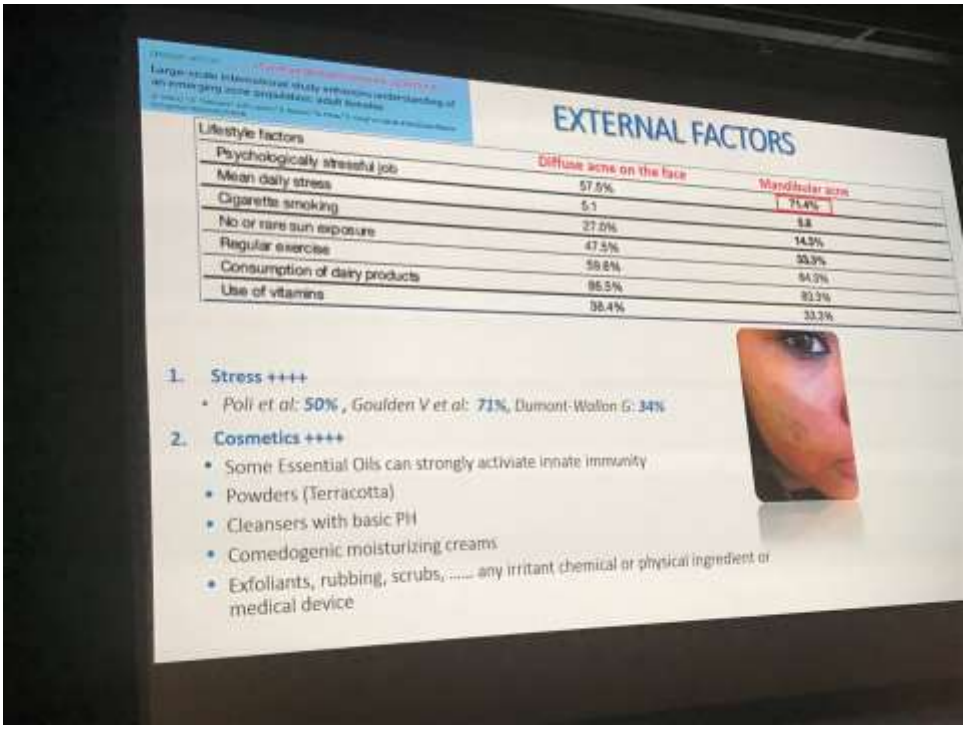
These tests should be obtained in the luteal phase of the menstrual cycle (within two weeks before the onset of menses). Excess androgens may be produced by either the adrenal gland or the ovary.

Hormonal treatment effective even in patient without hormonal abnormalities, especially those with menstrual flare.




THREE CLINICAL PROFILES
ONE IS SPECIFIC OF ADULT WOMEN
1. Predominant diffuse retentional lesions: hyper seborrhea with many small closed comedone
2. Predominant diffuse superficial inflammatory lesions (papulopustules): few comedone on the face
3. Chin acne: deep-seated, long-lasting nodules and cysts in the lower third of the face, jaw line and neck (15%)
1
2
3


PROFIL OF ACNE ADULT FEMALES
Hereditary factor: 57% of females
* Mother (37%), Father (41%), Siblings (45%)
High frequency of acne scars: 64% of females
* Acne scarring in the family:28.8%
Less severity compared to adolescent acne
* 85% mild to moderate acne
High level of Hyper seborrhea
Flare up before menstruation: 80% females
Two external factors: Stress ++++ and cosmetics ++
Active professional life



Hormonal influence

Table VII. Recommendations for hormonal agents

Estrogen-containing combined oral contraceptives are effective and recommended in the treatment of inflammatory acne in females
Spironolactone is useful in the treatment of acne in select females
Oral corticosteroid therapy can be of temporary benefit in patients who have severe inflammatory acne while starting standard acne treatment
In patients who have well documented adrenal hyperandrogenism, low-dose oral corticosteroids are recommended in treatment of acne

HORMONAL AGENTS

- 20-35 ug of ethinyl estradiol
- Low-dose prednisone (2.5 mg or 5 mg) or dexamethasone (0.25- 0.75 mg)
- Glucocorticoids and estrogens has been used in recalcitrant acne

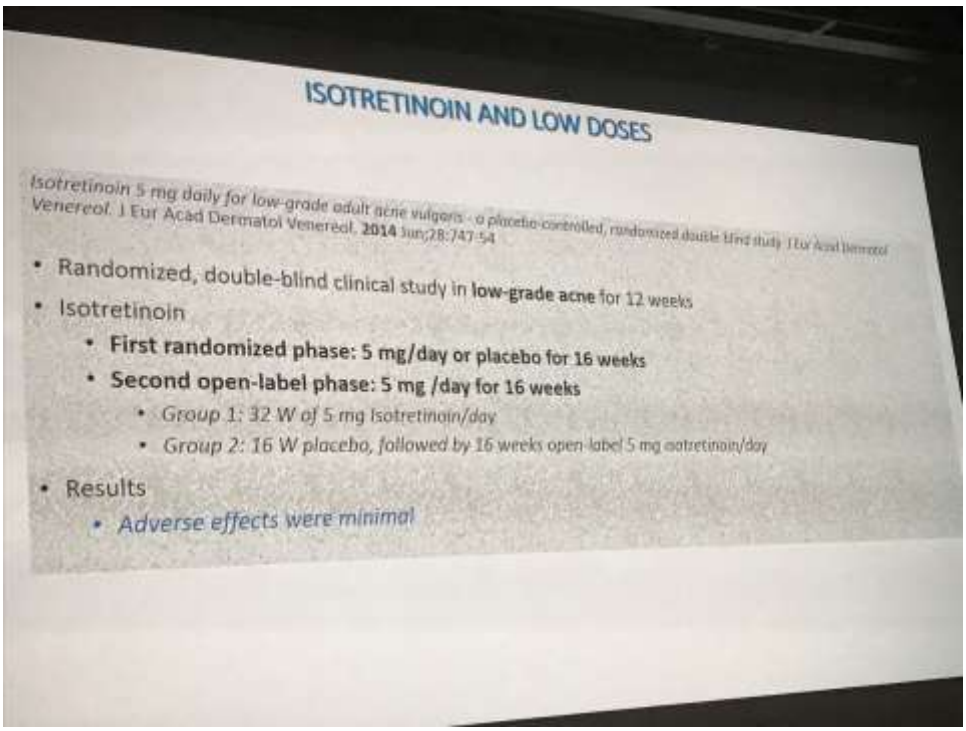
HORMONAL AGENTS

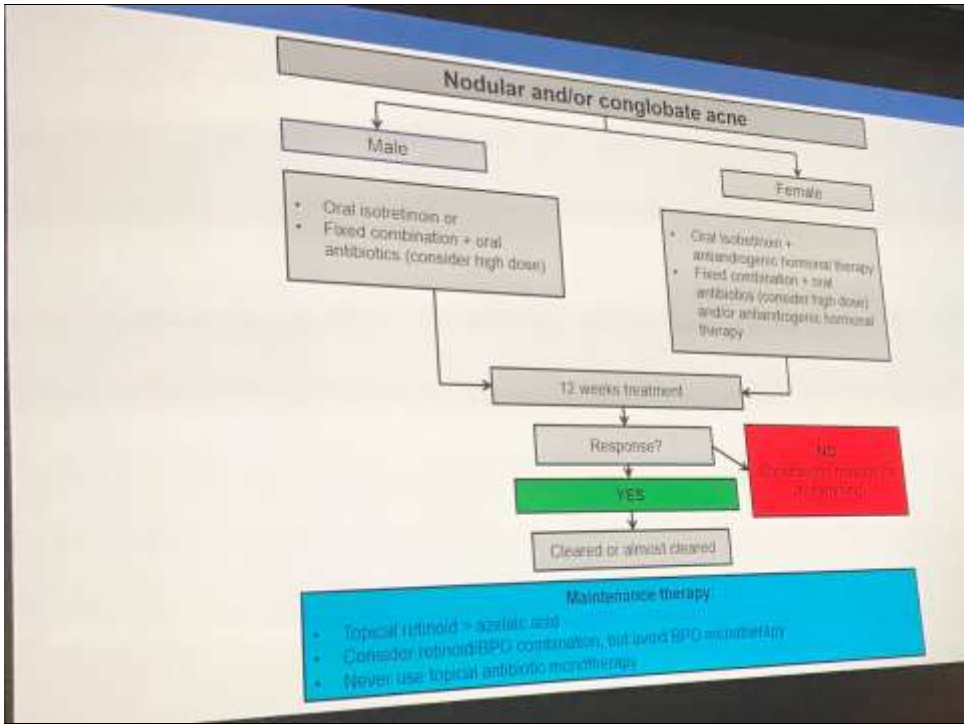
A unique combination oral contraceptive, Yasmin, combines 30 ug ethinyl estradiol with the 3 mg drospirenone.

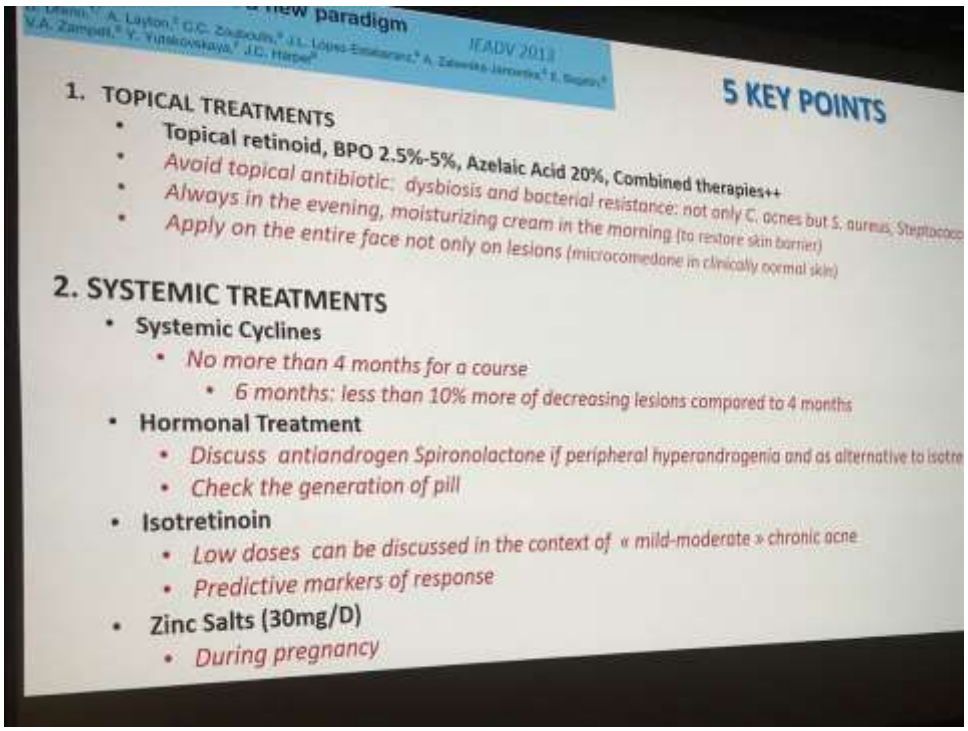
Spironolactone , 50 mg to 200 mg.

Cyproterone acetate ,Diane-35&50.


ADULT FEMALE ACNE
NEED SPECIFIC GUIDELINES
Clinical level
Late Onset of acne
Specific subtype: mandibular acne
Pathophysiological level
Peripheral hyperandrogenism
Chronic stimulation of Innate Immunity
Treatment level
Topical treatment
Avoid absolutely topical antibiotic
Maintenance Therapy
Systemic Treatment
Isotretinoin: Low doses: need to be confirmed
Hormonal treatment: Interest of 3rd and 4th generation pills and low doses of spironolactone
Need maintenance treatment
Take care of cosmetics
Represent only a paragraph in different national and international guidelines
Mentioned in the final Algorithm of EDF and Global Alliance Guidelines


ISOTRETINOIN AND LOW DOSES
Isotretinoin 5 mg daily for low-grade adult acne vulgaris - a placebo-controlled, randomized double blind study. J Eur Acad Dermatol Venereol. J Eur Acad Dermatol Venereol. 2014 Jun;28:747-54
Randomized, double-blind clinical study in low-grade acne for 12 weeks
Isotretinoin
First randomized phase: 5 mg/day or placebo for 16 weeks
Second open-label phase: 5 mg /day for 16 weeks
Group 1: 32 W of 5 mg Isotretinoin/day
Group 2: 16 W placebo, followed by 16 weeks open-label 5 mg isotretinoin/day
Results
Adverse effects were minimal


Nodular and/or conglobate acne
Male
Female
Oral isotretinoin or
Fixed combination + oral antibiotics (consider high dose)
12 weeks treatment
Response?
YES
Cleared or almost cleared
Maintenance therapy
Topical retinoid ± azelaic acid
Never use topical antibiotic monotherapy


JEADV 2013
5 KEY POINTS
1. TOPICAL TREATMENTS
Topical retinoid, BPO 2.5%-5%, Azelaic Acid 20%, Combined therapies++
Avoid topical antibiotic: dysbiosis and bacterial resistance: not only C. acnes but S. aureus, Streptococ
Always in the evening, moisturizing cream in the morning (to restore skin barrier)
Apply on the entire face not only on lesions (microcomedone in clinically normal skin)
2. SYSTEMIC TREATMENTS
Systemic Cyclines
No more than 4 months for a course
6 months: less than 10% more of decreasing lesions compared to 4 months
Hormonal Treatment
Discuss antiandrogen Spironolactone if peripheral hyperandrogenia and as alternative to isotre
Check the generation of pill
Isotretinoin
Low doses can be discussed in the context of « mild-moderate » chronic acne
Predictive markers of response
Zinc Salts (30mg/D)
During pregnancy

LASER AND LIGHT-BASED THERAPIES

- **Photodynamic therapy**
- **IPL**
- **PDL** preferentially targets oxyhemoglobin and induces photothermolysis of blood vessels, some believe it should be particularly effective in **treating inflammatory acne lesions**
- **1450-nm diode laser ,sebaceous gland destruction**

NEW EMERGING(2019)

- **The enzyme stearoyl coenzyme Adesaturase 1 (SCD1)** is a potential target for **reducing sebum production.**
- **Inhibition of SCD1** has beenshown to reduce the synthesis of monounsaturated fatty acids and the number of sebaceous glands in mouse skin.
- Several clinical trials of topical formulations of **SCD1** are ongoing.

NEW EMERGING(2019)

- **Nitric oxide releasing particles** are under investigation due to their potential to suppress the release of multiple cytokines from human monocytes and keratinocytes and to prevent **C. Acne induced inflammation.**
- In two phase 2 studies of the topical **nitric oxide releasing drug SB204**, the drug significantly reduced noninflammatory and inflammatory lesion counts in patients with mild, moderate, and severe acne compared with vehicle alone

NEW EMERGING(2019)

- **Anti-androgen cream (cortexolone 17a-propionate 1%)** was found to improve total and inflammatory lesions counts compared with placebo after 8 weeks of therapy.

Conclusion

- **Combination of a topical retinoid plus an anti microbial agent as first-line therapy.**
- **Oral isotretinoin 0.5 to 1.0 mg/kg/day, 20-week course**
- **Cumulative dose of 120 to 150 mg/kg**

Conclusion

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- oral isotretinoin 0.5 to 1.0 mg/kg/day, 20-week course
- Cumulative dose of 120 to 150 mg/kg
- oral isotretinoin with food
- 30% of patients relapsed

Conclusion

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- oral isotretinoin 0.5 to 1.0 mg/kg/day, 20-week course
- Cumulative dose of 120 to 150 mg/kg
- oral isotretinoin with food
- 30% of patients relapsed
- Spironolactone , 200 mg
- Isotretinoin 5mg
- Yasmin+Spironolactone 100 mg
- for 6 months.

THANK YOU