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Clinical Evidence. Practical Advice.

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Welcome to Skin Therapy Letter® US Family Practice Edition

The goal of this novel publication is to improve both diagnostic and therapeutic skills among primary care practitioners with regard to diseases and disorders of the skin, hair, and nails. The Editor and publishers feel that this is a critical educational endeavor, and one designed to improve overall patient care. Due to obvious constraints, graduate and primary care medical education often contain very limited exposure to or training in dermatology.[1] Despite this, those who deliver primary care are frequently called upon to manage skin maladies. Consider these facts:

- 5.3% of all medical office visits pertain to dermatological issues.[2]
- Only 33% of patients with skin problems see a board-certified dermatologist first.[3]
- Primary healthcare providers are the second most prolific purveyors of dermatological care in the US.[3]
- 20%–36.5% of patients presenting in a primary care setting have at least one skin problem.[4,5]
- Although skin problems may be secondary issues during a medical encounter, 60%–72% of the time the skin problem is actually the chief complaint and, therefore, the reason for seeking medical attention.[5,6]

These trends will likely persist as awareness of skin disease increases among the general population due to professional educational campaigns, media influences, high-profile personalities developing skin cancer, and direct-to-consumer medical advertising.

Limited direct access to board-certified dermatologists will also augment use of primary care services for skin care; direct dermatological access may be difficult due to managed care regulations and economic disincentives, very stringent documentation and preauthorization requirements, and a shortage of dermatologists in select geographic locales.[7] The trend toward "cosmetic procedures only" practices further reduces the pool of dermatologists available for medical consultation and care.

Despite the fact that primary care providers play a crucial role in delivery of cutaneous health care, there is ample evidence that they are inadequately trained in this field. Multiple comparative studies, summarized in a recent publication, clearly show a deficient ability of those in primary care to diagnose and treat skin disease in an optimal manner.[8] Moreover, keeping abreast of the latest therapeutic advances in such a narrow discipline is difficult for those charged with the overall health and welfare of their patients. Thus, we have the genesis of Skin Therapy Letter. It is our hope that this streamlined publication and its associated internet site (www.SkinTherapyLetter.com) will serve as methods to rapidly enhance your diagnostic and/or therapeutic skills in the realm of cutaneous medicine, as well as to provide tools to help you decide when expeditious dermatological referral is the most judicious action to take.

Ted Rosen, MD
Editor

References listed online at www.SkinTherapyLetter.com

Topical Acne Treatment

L. Kircik, MD

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Acne Vulgaris

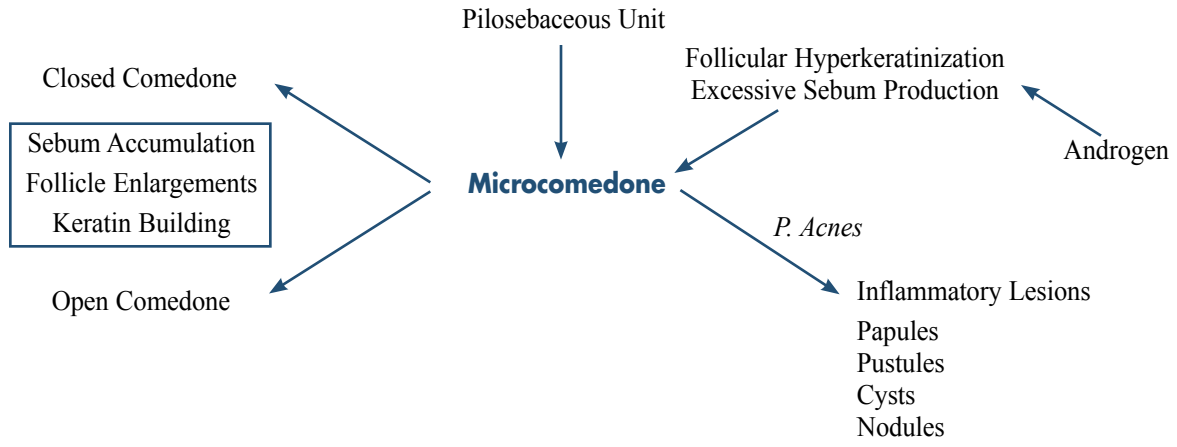
Acne vulgaris is a disorder of the pilosebaceous units located on the face, chest, and back. It affects up to 45 million Americans, mostly in the 15–24 year age group, and can cause a poor self image, withdrawal, and even depression and suicidal ideation. More than $100 million per year is spent on OTC acne products. Scarring and postinflammatory hyperpigmentation are the most important sequelae.

Treatment

The most important treatment goal is to minimize scarring by preventing further acne development. Patient compliance is also very important in acne treatment. Minimizing adverse events and ease of treatment will maximize patient compliance.

Pathophysiology of Acne Vulgaris

The microcomedone is the precursor of all lesions.



Classification of Acne

1. Noninflammatory
   a. Open comedones and closed comedones
   b. Treated with topical agents
2. Inflammatory
   a. Papules: erythematous small bumps <1.0cm
   b. Pustules: pus-filled, erythematous small bumps <1.0cm
   c. May not respond to topical agents alone. Topicals can be combined with oral agents.
3. Nodulocystic Acne
   a. Nodules
   b. Cysts
   } 1.0cm tender lesions
   c. Treated with oral agents

Topical Retinoids

- Tretinoin (Retin-A®, Retin-A® Micro)
- Tazarotene (Tazorac®)
- Adapalene (Differin®)

Topical retinoids are most efficacious at preventing microcomedone formation. They should be applied sparingly to all affected areas, usually at night. Irritation and dryness make topical retinoid application challenging. It is advisable to avoid nasolabial and melolabial folds. Some retinoids, such as tazarotene, can be used as a short-contact treatment to avoid irritation. Use of gentle cleansers, noncomedogenic moisturizers, and avoidance of alcohol-based products and astringents will help to increase the compliance.

Topical Antibiotics

- Erythromycin (Aknemycin®, ATS®)
- Clindamycin (Cleocin T®, Clindagel®, Evoclin® Foam)

Both agents have anti-inflammatory and anti-infective action; however, due to reports of bacterial resistance, use as monotherapy is not recommended. Combinations of different agents (e.g., in combination products) should be the first-line treatment for inflammatory lesions.

Combination Therapy

- Topical clindamycin 1% + 5% benzoyl peroxide (BPO) in moisturizing base (Duac®)
- Topical clindamycin 1% + 5% BPO (Benzaclin®)
- Topical erythromycin 3% + 5% BPO (Benzamycin®)

These combination products will fight both inflammatory and noninflammatory lesions (comedones). They will also help to prevent bacterial resistance. They may result in fabric bleaching.

- All patients with acne can benefit from topical therapy, except those receiving isotretinoin.
- Topical retinoids should be applied to the whole acne prone area. They should be thought of as preventing new lesions, rather than treating those that have already formed.
- For inflammatory acne, it is reasonable to use a combination topical therapy early on, such as a BPO/antibiotic combination. One can be used in the morning and the other in the evening.
- An adequate response to treatment can be measured in a few months, not weeks.
- Systemic therapy can be used if response is still poor after at least 3 months.

Therapy	Normalizes Keratinization or is Keratinolytic	Decreases *P. acnes*	Decreases Inflammation
Antibiotics		•	•
Retinoids	•		•
Benzoyl Peroxide	•	•	•
Azelaic Acid	•	•	

Table 1: Actions of topical treatments.

Importance of Vehicle in Topical Treatment

The role of vehicle in topical acne treatment is also very important.

- Glycerin – humectant
- Dimethicone – occlusive emollient

Combining these two products contributes to barrier restoration and will reduce adverse events such as dryness, peeling and irritation. Therefore, products containing these vehicles may be more tolerable for patients, in particular if they develop irritation with topical retinoids. The use of combination products will prevent emergence of antibiotic resistance.

Acne Surgery

Removal of noninflammatory lesions with a comedone extractor is helpful, but time consuming.

Cryotherapy

A spray of liquid nitrogen in moderate amounts or the application of slushed dry ice can be considered in the treatment of acne vulgaris. Periodic glycolic or salicylic acid peels also have benefits.

The Number One Reason for the Failure of Acne Treatment is Noncompliance

Management of the patients' expectations and compliance are crucial aspects of acne treatment. Disease chronicity and long-term treatment should be discussed at length during the initial consultation. A skin care regimen with gentle cleansers and moisturizers will ease these patients into their treatment program and increase compliance by decreasing dryness and irritation from topical medications.

Editor's Comment:

As Dr. Kircik notes, the microbe *P. acnes* remains central to the etiology of inflammatory acne lesions. Elucidation of the entire genome of this commensal organism has led to new insights into pathogenesis and to a new understanding of why certain therapeutic interventions are successful.[1] For example, the genome discloses that *P. acnes* is capable of producing glycocalyx material necessary to form a biofilm. In turn, this explains the relative resistance of the putative causative bacterium to topical antibiotics when given as monotherapy. The addition of benzoyl peroxide, which disrupts the biofilm-rich microenvironment, allows better penetration of a concomitant antibiotic. Disruption of the biofilm also increases the local oxygen tension, thereby creating a less satisfactory situation for *P. acnes,* a commensal anaerobe. Development of antimicrobial resistance when acne is treated with topical antibiotic monotherapy is a real phenomenon. Even more importantly, the genome discloses that *P. acnes* possesses the necessary intracellular mechanisms to pass on resistance to other bacteria. A recent study demonstrated that this may, indeed, happen under normal clinical conditions.[2] Thus, use of synergistic therapy (such as benzoyl peroxide along with an antibiotic) is truly appropriate. A recent innovative therapy, the use of high-intensity, visible blue light, is also justified by the genome-directed synthesis and secretion by *P. acnes* of a photo-target (porphyrin).[3,4] The treatment of acne may expand even further as modern technology, such as genetic sequencing, is brought to bear on this common and distressing disorder.

References are listed online at www.SkinTherapyLetter.com

A Summary of Approved Topical Treatments for Rosacea

G. Webster, MD, PhD

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Rosacea's cause is unknown; however genetic, environmental, vascular, and inflammatory factors have been identified as possible triggers (see Table 1).

Symptoms

- facial erythema and/or visibly dilated blood vessels
- papules and pustules
- burning or stinging (may be triggered by topical agents)
- swelling
- ocular and phymatous changes

Rosacea Subtypes

1. Vascular (erythematotelangiectatic)

- prolonged flushing or permanent vasodilation and telangiectasia[1]

2. Papulopustular

- persistent central facial erythema; associated inflammatory lesions (papules and pustules)

3. Phymatous

- sebaceous hyperplasia with fibrosis.

  - the nose is the predominant affected area

4. Ocular (underrecognized)

- affects nearly 60% of rosacea patients[2]
- sensation of dry eye or irritation or photophobia
- interpalpebral conjunctival hyperemia[3]

Quality of Life

More than 14 million people in the United States are affected, and 60% are adults under the age of 50.

- Nearly 70% of patients report low self-esteem; 41% avoid public contact due to their condition.
- 70% of severely affected patients report that it adversely affects their professional relationships.
- 30% report that they would miss work because of their condition.[4]

Treatment

There is presently no cure, so management and treatment focus on symptom reduction. The National Rosacea Society stresses the importance of early diagnosis and treatment.[5] Subtypes 1 and 2 (as seen in Figures 1 and 2, which are online at www.skintherapyletter.com) are often treated with topical agents, whereas subtypes 3 and 4 require more intensive therapies like systemic antibiotics and sometimes surgery. **Laser or light may be needed for reduction of the vascular component.**

Avoid Trigger Factors

- Patients diagnosed with subtypes 1 and 2 are most susceptible to these factors.
- Avoidance alone will not cure the condition, but it may help to alleviate rosacea flare-ups.
- While not all trigger factors apply to every patient, most are affected at least by some of them.

Environmental	Chemical/Other	Dietary	Cosmetic
Sunlight	Medications	Spicy foods	Astringents
Humidity	Caffeine withdrawal	Dairy products	Toners
Heat	Stress/anxiety	Liver	Soap and shampoo
Strong winds	Exercise	Chocolate	Exfoliating agents
Cold weather	Menopause	Vanilla	Makeup
	Chronic cough	Certain fruits & vegetables	Perfume/cologne
	Genetic	Soy sauce	Moisturizers
	Demodectic mites	Vinegar	Hairsprays
		Alcoholic beverages	Sunscreen
		Piping hot food & beverages	Shaving lotions

Table 1: Rosacea Trigger Factors

Metronidazole

Metronidazole is the only topical agent validated by multiple well-controlled trials.[6-15]

- It is a broad-spectrum imidazole agent that exhibits antimicrobial and anti-inflammatory effects.
- It may interfere with neutrophil release of reactive oxygen species.[14]
- It is available in a 0.75% cream (MetroCream™), 0.75% lotion (MetroLotion™), 1% cream (Noritate®) and 1% gel (MetroGel™), which replaced the no-longer available 0.75% gel.
- Metronidazole is widely recognized as the gold standard for treating rosacea.[16]
- Usage
  - 0.75% formulations are twice-daily regimens.
  - 1% formulations are once-daily, which may lead to better patient compliance.

Adverse Effects

Mild-to-moderate adverse effects, such as stinging, burning, drying, and itching.[17] A cumulative irritation study demonstrated that metronidazole gel 1% is milder than metronidazole gel 0.75% and azelaic acid gel 15%.[18]

A comparative trial with metronidazole gel 1% used once daily and azelaic acid gel 15% used twice daily showed equal efficacy in inflammatory lesions, global severity, and erythema. Patients reported that they were less bothered by side-effects with metronidazole gel 1% than with azelaic acid 15%.[19]

Azelaic Acid

It is a naturally occurring dicarboxylic acid with antioxidant and anti-inflammatory effects.[20]

- It is available in a twice-daily, 15% gel (Finacea®).
- Inflammatory lesion counts were reduced 51%-58% and improvement in erythema was 44%-46% in two 12-week studies with a combined total of 664 patients.[20]

Adverse Effects

Local skin irritations, such as facial burning, stinging, and pruritus have been reported.[21]

Sodium Sulfacetamide 10% and Sulfur 5%

This formulation is available as a cream (Suphera™ and Rosac®), lotion (Sulfacet-R® and Klaron®), gel (Rosula®), suspension (Plexion®), and cleanser (Rosanil®) that can be used as monotherapy or in combination therapy with other agents, like metronidazole. The typical treatment regimen is twice daily.[2,22,23]

Adverse Effects

Allergic reactions appear to be related to the sulfa drug and include swollen eyes, facial dryness, pruritus, hives, and increased erythema. Most adverse events are mild.

Role of Cleansers and Moisturizers

Skin maintenance is an important part of controlling rosacea. General skin care involves the use of the following:

- therapeutic non-soap cleansers to minimize the potential irritation, while improving hydration[24]
- moisturizers, which hydrate the stratum corneum and restore its ability to retain moisture[25]
- broad-spectrum sunscreens are important to avoid triggering long-term photodamage[26]

Conclusion

Today, diagnosing and treating rosacea remains a challenge. More studies are necessary to provide additional insight on drugs currently available as well as possible future agents. The ultimate goal is to provide each patient with a treatment regimen best suited for his or her individual needs.

Editor's Comment:

As recently noted by Landow, the etiology of rosacea remains an enigma and, as such, the disorder poses a frustrating challenge for both patients and healthcare providers alike.[1] Aside from cosmetic distress, untreated disease can lead to permanent disfigurement in the form of soft tissue hypertrophy, vision-disturbing ocular symptoms, and even severe mental aberrations such as major depression.[2] Thus, timely diagnosis and prompt administration of therapy is imperative. Triggering factors, as listed in this synopsis, are quite idiosyncratic. Several, one, or none of the many "triggers" listed may apply to any given patient. The relevance of any potential trigger factor may be elucidated by a detailed history; conversely, it may be discovered only by trial and error, as factors are sequentially eliminated.

Topical therapy requires daily application of one or more agents to the entire face. For some patients, this may be difficult to integrate into a hectic or erratic schedule. For others, topical therapy may result in transient or persistent adverse events (such as stinging and burning). However, the wide spectrum of therapeutic options available, including the many different types of formulations, almost always insures that some available medication will be tolerable. Moreover, for other patients, topical therapy is preferable to any systemic medication. Mild-to-moderate vascular and papulopustular rosacea is most amenable to topical therapy.[3] The Editor believes that topical therapy should always be entertained and at least offered to most patients. Recent development of phototherapeutic systems that may eliminate residual erythema represent an exciting forefront in rosacea management.[4] We will discuss systemic therapies, including new advancements, in a future issue of *Skin Therapy Letter - US Family Practice Edition.*

References are listed online at www.SkinTherapyLetter.com.

Actinic Keratoses

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Actinic Keratosis

The actinic keratosis (AK) is a common lesion induced by ultraviolet light that represents the earliest manifestation of squamous cell carcinoma (SCC) of the skin.

- The name means sun-induced (actinic) scaly, thickened growth of the skin (keratosis).
- It is seen almost exclusively in Caucasians due to their fair skin and sun sensitivity.
- The incidence increases closer to the equator and correlates with outdoor occupation.
- It is typically seen on chronically sun-exposed parts of the body, i.e., the face, the scalp of bald men, the back of the hands, and the forearms.
- It can arise in other parts of the body, if those areas receive significant sun exposure.
- It has been described as a "precancer" but molecular and histologic features suggest it exists in a continuum with invasive SCC.
- It has recently been proposed that AK be renamed to KIN, or keratinocytic intraepithelial neoplasia.

There is a roughly linear relationship with sun exposure and the development of AKs throughout life, as opposed to the development of melanoma, which correlates with recreational sun exposure prior to the age of 20. A small percentage of AKs can and do progress to become invasive SCC, although the fate of any one lesion is impossible to predict.

Histology

- AKs are characterized by partial thickness dysplasia of the epidermis.
- Cellular atypia is present, and mitotic figures may be seen upwards from the basal layer.
- Lesions are the same as those seen in SCC, differing only in the degree to which they are present:
  - AK: changes occupy only part of the epidermis and do not extend down hair follicles.
  - SCC: *in situ* is characterized by full-thickness involvement of the epidermis and extension down hair follicles. Invasive SCC penetrates the basement membrane and invades the dermis.

Clinical Presentation

- The AK begins as a small rough spot on sun-exposed skin; better felt than seen.
- Over time, the lesions become larger and more visible, most often as scaly pink macules.
- Most lesions are a few millimeters in diameter, but some can reach >2cm in diameter.
- Variants include pigmented (brown) lesions, and lesions where the hyperkeratosis is so pronounced that a horn-like projection arises from the skin.
- Multiple AKs may develop within a given anatomic area or cosmetic unit (e.g., cheek, forehead).
- As the lesions enlarge, they may collide and become confluent.

An AK may follow one of three paths:

- It may remain unchanged.
- It may spontaneously resolve.
- It may progress to an invasive SCC.

The estimated frequency of conversion is estimated to range from as low as 0.1% to as high as 10%–16%. While the exact progression rate is uncertain, it is clear that the rate is not zero. Eradication of lesions to prevent invasive SCC seems justified.

Treatment

Treatment may be broadly divided into destructive and medical:

- Destructive therapies use a physical modality to kill the AK cells, hopefully limiting damage to the surrounding normal skin. Also referred to as "lesion-directed" therapy.
- Medical therapies use a pharmacologic approach to destroy the AK cells and identify and treat subclinical lesions in the surrounding skin. Also referred to as a "field-directed" therapy.

Destructive Therapies

For >90% of treated AKs, destructive therapy is used, which is most often cryosurgery with liquid nitrogen.

- Liquid nitrogen is -195.8°C and may be directly applied to the skin.
- Once the skin temperature is lowered to around -40°C the keratinocytes of the epidermis (and the AK) will die.
- The dermis, including collagen, blood vessels, and nerves, is relatively resistant to cold.
- Melanocytes are sensitive to cold, so cryosurgery tends to often leave permanent white spots.

Other destructive methods include curettage and shave scalpel excision. As these methods may cause scarring they are generally used only when specimens are needed for histological examination to rule out SCC.

Medical Therapies

- Include topical creams and lotions that can treat large areas.
- Indicated for patients with many lesions.
- Can also treat subclinical lesions, i.e., early lesions too small to clinically detect.
- Weeks to months of treatment are usually required.
- Can produce significant, though temporary, inflammation and discomfort.

There are currently four topical medications used for the treatment of AKs:

- 5-fluorouracil (Efudex®, Fluoroplex® and Carac®)
  - Used for almost 4 decades with great success.
  - Associated with inflammation and discomfort that resolves once treatment is finished.
  - Available formulations include a 5% cream or solution, a 2% solution, a 1% cream or solution, and a micronized 0.5% cream.
  - The various concentrations seem to be equally effective.
- Imiquimod cream (Aldara™)
  - Is an immunomodulator, nonantimetabolite, chemotherapeutic agent.
  - Enhances a local immune response by upregulating a variety of cytokines.
  - Induces a non-specific immune response via the interferons and natural killer cells, and a specific immune response via T cells.
- Diclofenac gel (Solaraze™)
  - Is a nonsteroidal anti-inflammatory drug (NSAID) that eliminates AKs in an unknown way.
  - Produces less inflammation than other agents listed.
  - Requires a rather lengthy 3-month course of therapy.
- Delta amino levulinic acid solution (Levulan® Kerastick®) followed by activation with visible light (photodynamic therapy)
  - May be performed with a solution of delta amino levulinic acid (ALA).
    - An intermediary in the heme biosynthetic pathway
    - Accumulates in the dysplastic cells of the AK following topical application
    - Inside keratinocytes converts to protoporphyrin IX, a potent photosensitizer.
  - After topical application, this conversion is allowed to take place over one to many hours, then the protoporphyrin IX is activated by exposure to visible light.
  - Generates reactive oxygen species and, ultimately, selective dysplastic cell death.
  - One or two such treatments are highly effective.
  - Produces a sunburn-like reaction lasting from a few days to >2 weeks.

Conclusion

Actinic keratoses are a common, and easily treated, precursor to an invasive SCC. Destructive therapies are appropriate for a few lesions, while a medical approach is reserved for patients with many lesions.

Editor's Comment

AKs are actually quite controversial in the dermatological world. Some authorities feel that AKs are best considered "premalignant" and clearly distinguishable from frank SCC.[1] Other authors suggest that there is a reproducibly gradable clinicopathologic continuum between AKs and SCCs.[2] Yet other influential dermatologists firmly believe that AKs are already true SCCs.[3] The point of this ongoing debate is whether aggressive field-directed intervention is justified, conservative lesion-directed therapy is optimal, or treatment for AKs is even necessary at all. Although AK eradication is certainly an accepted standard of care, some have questioned, on pharmacoeconomic grounds, whether destroying the millions upon millions of incident AKs per year really prevents substantial morbidity and/or mortality.[4]

As Spencer points out in this synopsis, the practitioner can never predict which, if any, AK lesions will eventuate into an SCC with metastatic potential. Thus, clinical management dictates lesion ablation to avoid the worst-case scenario. However, the expectations of patients in the "baby-boom" generation are much different from those or prior generations, in that they expect such ablation to be carried out with rapid wound healing and minimal cosmetic alteration.[5] Hypopigmentation and/or scarring, which may accompany lesion-directed therapy (especially cryosurgery), is best avoided by utilizing one of the field-directed modalities. Unfortunately, field-directed therapies take longer to accomplish, require several to multiple office visits for monitoring purposes, carry a larger economic burden, and may be associated with relatively severe inflammation. Thus, all AK treatment options possess both advantages and limitations.

The best approach is a pragmatic one. The patient with few AK lesions is most conveniently and cost effectively treated with a destructive technique (cryosurgery or curettage with light desiccation). Those with many AKs are candidates for medical therapy (such as 5-fluorouracil, imiquimod or diclofenac).[6]

Emerging therapies beyond the scope of this synopsis, but worth watching for, include total laser resurfacing and chemoprevention with systemically administered NSAIDs.[7,8]

References are listed online at www.SkinTherapyLetter.com.

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Target Audience:

Family Physicians and Primary Care Physicians

Educational Objectives:

At the conclusion of this activity, participants should be able to:

1) effectively diagnose rosacea, acne, and AK.
2) prescribe appropriate medications for the treatment of these conditions.
3) apply effective treatment for these conditions.

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