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## Systemic Therapy for Rosacea

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### ABSTRACT

*Rosacea is a common condition that affects people of all races. In addition to the visible aspects of this disease, it can have a psychosocial impact that must be evaluated when considering the treatment options. More aggressive and innovative uses of existing oral agents have resulted in novel therapeutic approaches, which can provide long-term therapy and sustained remission.*

**Key Words:** Rosacea, Erythematotelangiectatic Rosacea, Papulopustular Rosacea, Phymatous Rosacea, Ocular Rosacea, Granulomatous Variant

Rosacea is a common disorder that is thought to affect 13-14 million people in the US alone.<sup>1,2</sup> It is likely that the actual number is substantially higher. Rosacea affects all races, although erythema may be less prevalent in patients with skin types IV and V. The rate of occurrence appears to be higher in women; however, men are more likely to develop phymas. Patients are most often diagnosed with this condition in their 30s-50s.

To truly understand the effects of rosacea on patients, the psychosocial impact must be evaluated along with the visible aspects of this disease. For many of our patients, the stigma of a "drinker's nose" and the social and professional isolation that can result from low self-esteem is far more significant than the clinical reality.

Contributing to the frustration experienced by patients with rosacea is the fact that as clinicians, we do not truly treat rosacea, but rather manage it. We cannot offer patients cures, simply improvements. As with all chronic conditions, continual therapy inevitably leads to non-adherence. The benefits derived from a combination of both medical and psychological approaches cannot be overemphasized. The overall objective is the improvement of the quality of life of patients, and in 2007, this goal is easier to attain thanks to topical medications that reduce skin irritation. Furthermore, with the advent of safer, once-daily systemic medications, it is possible to liberate patients from the use of topical products.

### Classification of Rosacea

Rosacea is a condition characterized by a constellation of symptoms including central facial erythema and telangiectasias, papules and pustules, granulomatous nodules, phyma formation, and ocular changes. The disorder is capricious with flares and remissions occurring without rationale.

For the task of discussing therapy, rosacea is best viewed as a collection of several conditions with a common name. Although many patients have polymorphic disease, most have one predominating feature.

The most commonly used classification system is based on predominant lesion morphology and was developed by a committee of the National Rosacea Society and published in 2002.<sup>3</sup> Patients are classified as having one of four types of rosacea: erythematotelangiectatic, papulopustular, phymatous, or ocular with a variant form referred to as granulomatous. Individual patients may straddle one or more subtypes, but this system allows us to determine therapy based on similar lesion types. Therapeutic options for the various lesion types are easily categorized and there are few medications or modalities that are significantly effective in more than one category.

## *Pathophysiology of Rosacea*

Our lack of understanding with regard to the pathogenesis of rosacea hampers our therapeutic efforts. Still unclear at this time is the fundamental issue of whether or not the papules and pustules are based in the follicle. There is a growing consensus that bacterial infection does not play a role in rosacea etiology. The neurologic or hormonal mechanisms that may generate the flushing reaction and phyma formation are similarly unknown. It is also unclear if accumulated sun damage, which bears many biochemical and clinical similarities to vascular rosacea, is involved in its pathogenesis.

What is known is that inflammation plays an important role in lesion formation. Inflammatory cells release proinflammatory cytokines and degradative enzymes that induce angiogenesis and damage dermal constituents.<sup>4</sup>

The outcome of our poor understanding of its pathogenesis is that treatment has been traditionally based on disease endpoints rather than targeting the underlying anomalies. Inflammation is treated with anti-inflammatory agents, flushing with vasoconstrictors, and telangiectasias with laser and light therapy. Until recently, papules and pustules were treated with antibiotics and no target organism.

## *Oral Therapeutic Options*

### **Antibiotics**

Oral antibiotics have been used off-label for the treatment of rosacea since the 1950s because it was believed that microorganisms were causative. We now know that there is little to no evidence supporting this premise. Although not curative, the observed benefits of oral antibiotic treatment in patients with rosacea have made clinicians and patients reluctant to exclude these agents from their therapeutic armamentarium, much less to downgrade them from their first-line status.

Due to the chronicity of this disease, antibiotic use is often long-term and can produce side-effects. Furthermore, overuse of antibiotics is associated with the emergence of resistant strains of bacteria that have the potential to result in adverse global health consequences.

### **Tetracyclines**

Tetracycline received US FDA approval in 1952 and the derivatives doxycycline and minocycline soon followed in 1966 and 1972, respectively. At the time of their introduction, they were known to be bacteriostatic and have broad-spectrum action. Since then, we have come to recognize the anti-inflammatory properties of the tetracycline class of antibiotics.

Tetracyclines are known to down-regulate the production of proinflammatory cytokines such as IL-1 and TNF-alpha.<sup>5</sup> They also inhibit neutrophil chemotaxis and the production of nitric oxide, reactive oxygen species, and matrix metalloproteinases (MMP).<sup>6,7</sup> This ability of tetracyclines to modulate the inflammatory response pathway, reducing the

inflammatory response, is believed to be the rationale for its effectiveness in treating rosacea.<sup>5</sup>

Tetracyclines are highly effective for papulopustular rosacea, requiring only 3-4 weeks of treatment for substantial improvement. Tetracycline 250-1000mg q.d., doxycycline 100-200mg q.d., and minocycline 100-200mg q.d. are most common. Use of oral tetracyclines until clinical improvement is seen, followed by a transition to topical antibiotics offers an alternative therapeutic regimen. There are patients for whom low-dose, long-term use of antibiotics are necessary to maintain control of their rosacea.

Long-term treatment with antibiotics is problematic for numerous reasons including significant side-effects.<sup>8-10</sup> Oral use of tetracyclines can result in disorders such as candidal vulvovaginitis, gastrointestinal distress, and even pseudotumor cerebri. Treatment with doxycycline can result in photosensitivity, and minocycline in vertigo and blue dyspigmentation. Minocycline has also been implicated in the development of lupus-like syndromes and hypersensitivity reactions. Of world-wide importance is the concern regarding emerging antibiotic resistance due to over/ misuse of antibiotics.

Anti-inflammatory dose doxycycline (20mg doxycycline hyclate) was FDA approved in 1998 for the treatment of adult periodontitis. The labeling permits continuous use for up to 12 months, and as such it is the only tetracycline approved for long-term use. It has been shown to be effective in treating papulopustular rosacea with a low incidence of adverse effects. Bikowski treated 50 patients with all types of rosacea and, at 4 weeks, noted an 80%-100% improvement in inflammatory lesions, and a 50% reduction in erythema.<sup>10</sup>

Although doxycycline has been shown to be highly effective, perhaps its major contribution is that dosage at 20mg results in sub-antimicrobial blood levels. Several studies have reported no effect on antibiotic susceptibility patterns in up to 18 months of continuous therapy and in 9 months post-treatment.<sup>12-14</sup>

Golub, in 1998, showed that doxycycline hyclate (Periostat®, CollaGenex) had anti-chemotactic activity, was a scavenger of reactive oxygen species and inhibited the enzyme MMP from being released.<sup>12</sup> Of primary importance is the ability of doxycycline hyclate to inhibit activation of the MMP-2 and MMP-9 enzymes that break down the capillary vessel basement membrane.

In 2006, a once-daily controlled-release formulation of doxycycline monohydrate became available (Oracea®, CollaGenex Pharmaceuticals). As the first FDA-approved oral treatment for rosacea, the once-daily 40mg capsule combines 30mg immediate-release and 10mg delayed-release doxycycline. The low dose remains below the antibiotic threshold and the controlled release allows for once-daily dosing. Acting as an anti-inflammatory medication rather than an antibiotic, controlled-release doxycycline does not exert selective pressure on microorganisms and as such does not cause bacterial overgrowth (i.e., folliculitis, vaginal

candidiasis) or encourage the development of bacterial resistance. Clinical studies have shown the formulation to be both efficacious and safe.<sup>15</sup> With once-daily dosing, compliance should also be improved.

### Macrolide Antibiotics

Erythromycin is an effective antibiotic in the treatment of papulopustular rosacea, but its use is often limited by GI distress. Erythromycin in doses of 250-1000mg/day is generally used in patients who are intolerant to tetracyclines and in pregnant women in whom tetracyclines are contraindicated.

Second generation macrolides such as clarithromycin and azithromycin have been shown to work faster and with less GI distress than erythromycin.<sup>16</sup> One study that followed patients for 3 years showed that subjects taking clarithromycin required less treatment time per year than those taking doxycycline (10.2 weeks/yr vs. 14.6 weeks/yr).<sup>17</sup> A 12-week trial of azithromycin in tapering doses showed an 89% reduction in inflammatory lesions.<sup>18</sup>

The relatively small advantages of the second generation macrolides, however, need to be weighed against the cost differential in the US of a 30-pill supply: erythromycin enteric coated capsules \$8.99, clarithromycin \$107.49, and azithromycin \$214.95.<sup>19</sup>

### Antibiotic Resistance

In the last decade, there has been increasing concern over the prevalence of antibiotic resistance. Dahl reported the rate of antibiotic-resistant *Propionibacterium acnes* (*P. acnes*) is up to 60%.<sup>20</sup> Globally, antibiotic-resistant *P. acnes* increased from 20% to 62% from 1978-1996.<sup>21</sup> European studies saw increases of 20% and 50% for tetracycline and erythromycin resistance respectively.<sup>22,23</sup> Consequently, there are concerns that increasing *P. acnes* resistance would result in a reduction in treatment success over time in rosacea patients.

Even greater cause for concern is the ability of *P. acnes* to transfer resistance to other, more pathogenic bacteria. Levy evaluated the long-term (>6 months) use of antibiotics in 105 acne patients.<sup>24</sup> He found that 85% of patients cultured positive for tetracycline resistant *Streptococcus pyogenes* in the oropharynx compared with 20% in the control group. Margolis, et al. suggested that this was not purely of academic interest, but translated into actual increase in disease.<sup>25</sup> In a large, retrospective study, an increase in upper respiratory infections in acne patients treated with either topical or oral antibiotics for greater than 6 weeks was seen. With the recent epidemic of methicillin-resistant *Staphylococcus*, tetracycline resistance has alarming implications.<sup>26,27</sup>

Concerns about resistance have resulted in the suggestion by several authors that long-term use of antibiotics be discontinued in acne therapy,<sup>21,28,29</sup> and serves as an even more appropriate recommendation in rosacea where there

is no evidence of a microbial pathogenesis. Because bacterial resistance is not as much of a concern, the use of anti-inflammatory dose doxycycline and other non-antibiotic alternatives in the treatment of rosacea is preferable whenever clinically appropriate.

### Metronidazole

Although effective in the treatment of rosacea, metronidazole has been associated with potential (although rare) side-effects such as neuropathy and seizures.<sup>30</sup> Alcohol abstinence is required during use to avoid a disulfiram-like reaction and headache.<sup>31</sup> Although rarely used in the US, oral metronidazole is prescribed frequently in Europe for long-term therapy of rosacea at doses of 200mg b.i.d.<sup>31-34</sup> In a double blind study of patients with papulopustular rosacea, it was shown to be as effective as oral oxytetracycline 250mg b.i.d.<sup>35</sup> Pregnancy category B labeling makes it an option for pregnant women.

### Isotretinoin

Isotretinoin is highly effective in the treatment of rosacea. It is one of the few medications that is capable of treating more than one subtype of disease. Onset of action is slower than that seen with the use of oral antibiotics.<sup>36,37</sup> In 1981, Nikolowski and Plewig showed that treatment resistant patients taking isotretinoin experienced fewer papules and pustules, a reduction in erythema, and decreased nasal volume.<sup>38</sup> Irvine, et al. demonstrated that this drug could halt rhinophyma by diminishing sebaceous gland size and number.<sup>39</sup>

More studies are needed to determine appropriate dosing schedules as well as optimal treatment duration. Unlike in acne vulgaris, it is not clear that isotretinoin can produce a permanent remission in rosacea. Schmidt and Raff documented remissions lasting up to 2 years after a course of isotretinoin.<sup>40</sup> More recently, Erdogan, et al. utilized low-dose isotretinoin at 10mg q.d. for 4 months and showed significant reduction in inflammatory lesions, erythema and telangiectasia at 9 weeks.<sup>37</sup>

In our continuing search for a therapy that does not result in antibiotic resistance, isotretinoin may be a viable alternative, especially in males and older women past child-bearing years. Low dose (10mg q.d. or q.o.d.), long-term use of isotretinoin can result in minimal risks of side-effects. Birth defects, however, are possible at any dose of this drug; low dose does not mean low vigilance.

### Dapsone

Reports in the literature support using dapsone in severe, refractory rosacea.<sup>41</sup> It is particularly helpful in patients for whom isotretinoin is contraindicated.

### Drugs That Antagonize Flushing

Many anecdotal reports exist regarding the use of agents that antagonize the flushing reaction, including vasoconstricting agents, and drugs that alter flushing



reactions in response to emotional stimuli.

Beta blockers in low doses (i.e., nadolol,<sup>9</sup> naloxone,<sup>42</sup> ondansetron,<sup>43</sup> aspirin,<sup>44</sup> and numerous selective serotonin reuptake inhibitors<sup>19</sup>) have been reported in isolated cases to be effective. However, there is no evidence-based research to support their use.

Craige and Cohen recently revisited the use of propranolol in the control of flushing and blushing.<sup>45</sup> At starting doses of 10mg t.i.d., none of their nine patients improved. Six of nine patients improved when doses were escalated to 20-30 mg t.i.d. At such high doses, three patients withdrew from the study due to side-effects. This study shows that the perceived ineffectiveness of beta blockers may be due to inadequate dosing.

Clonidine has also been reported to improve flushing and blushing reactions at doses of 0.05mg b.i.d.<sup>46</sup> At this dose there was no reduction in blood pressure, but lower baseline malar temperature may have been reduced by peripheral vasoconstriction. Although some patients do remarkably well on clonidine, responders are not clinically identifiable before treatment. Since control of this feature of rosacea is so difficult, a trial course may be indicated.

### *Therapy Based on Rosacea Subtype*

#### **Erythematotelangiectatic Rosacea**

The erythematotelangiectatic subtype of rosacea is the most difficult to treat. There is little evidence that topical or oral antibiotics have any role in the treatment of erythema, telangiectasias and flushing-blushing reactions. Isotretinoin may improve erythema resulting from inflammation, but this effect may be transient. Drugs that antagonize flushing may be helpful in some patients. Vascular laser and light therapy is the most effective modality in this subtype.

#### **Papulopustular Rosacea**

The papulopustular type of rosacea is the easiest subtype to treat. Most of these patients respond readily to topical medications such as metronidazole, benzoyl peroxide, clindamycin, erythromycin, and azelaic acid. In several studies, topical medications were shown to be equally effective to oral medications although therapy may take longer to be effective.

Since 2006 there has been a paradigm shift in the therapeutic decision-making process for treating rosacea. In the past, topical agents were considered as first-line therapy, and oral agents were introduced only when topical medications were ineffective, or were used in patients for whom immediate response was paramount. With the advent of once-daily, non-antibiotic dosing of doxycycline, oral therapy has become more commonly prescribed as first-line treatment. Often oral and topical antibiotics are used in combination; the resulting effect may be synergistic. Ultimately the patient may be converted to topical therapy alone for maintenance purposes. However long-term, anti-inflammatory dose doxycycline offers a viable alternative.

Isotretinoin is highly effective in this type of rosacea, especially given that low-dose, long-term therapy is an option particularly in men and women of nonchildbearing potential.

Dapsone may be necessary in refractory rosacea or in a patient for whom isotretinoin is contraindicated.

#### **Phymatous Rosacea**

Surgical or laser ablation is often necessary to eradicate existing lesions of significant size. Isotretinoin has been reported to halt the progression of rhinophymata and to shrink overall volume of phymata by reducing the size of the sebaceous glands, but it does not appear to be curative.<sup>37,39,40,47-50</sup>

#### **Ocular Rosacea**

Mild, chronic ocular rosacea responds well to topical agents and eyelid hygiene. More significant disease responds promptly and substantially to virtually any oral antibiotic. Tetracyclines, because of their safety profile, are most often used.<sup>51,52</sup> Isotretinoin use may improve the more severe presentations of ocular rosacea, including coloboma formation and corneal erosions. Potential side-effects for this type of rosacea include dry eyes and gritty irritation during therapy.

#### **Granulomatous Variant**

The granulomatous variant of rosacea is treated in the same manner as papulopustular rosacea reviewed above. Severe disease also responds to the use of oral and intralesional corticosteroids.

#### **Conclusions**

Until recently, there had been little change in the systemic treatment options for rosacea over the last several decades. In 2007, more aggressive and innovative uses of existing oral agents have resulted in novel therapeutic approaches. The development of anti-inflammatory dose doxycycline monohydrate is an intriguing alternative to long-term or episodic use of full-dose antibiotics. Once-daily dosing with the controlled-release formulation of doxycycline monohydrate can be expected to improve compliance and therefore efficacy. Furthermore, anti-inflammatory dose doxycycline and isotretinoin are helpful modalities for preventing treatment failures. Agents with good or acceptable safety profiles allow for long-term therapy and provide sustained remission. More importantly, the use of oral agents that do not increase the likelihood of future bacterial resistance is of global importance.

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# An Algorithm for the Reconstruction of Complex Facial Defects

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## ABSTRACT

*Dermatologic surgeons are often faced with the repair of complex facial defects following Mohs micrographic surgery. While the size or absence of critical tissue layers may be daunting, the reconstruction of these complex defects follow similar principles to those for the closure of smaller, simpler defects. There are several issues specific to these closures including whether to delay closure in order to allow wound contraction, thus decreasing the size of the wound. Yet, if the defect is adjacent to a fixed anatomic structure, this may not be an option. The tumescent technique allows for effective anesthesia over large surface areas. Although choosing a method of closure may be specific to the anatomic area, if possible, it is best to choose a "workhorse" flap, e.g. multiple flaps or a flap and a full thickness skin graft. Occasionally, a tunneled pedicle flap may be appropriate. For large areas an artificial skin substitute may be necessary. While tissue expansion has a number of disadvantages, it may be the only option for large defects in immobile anatomic regions. While it would be optimal to close every Mohs defect, it is important to know when to refer a reconstruction that may require general anesthesia and/or hospitalization.*

**Key Words:** Tumescent, Bilobed, Paramedian, Mohs Defect

Increased public awareness of skin cancer, improved access to dermatologists, and greater availability of Mohs micrographic surgery have combined to decrease the average size of tumors and post-surgical defects. Yet, for a variety of reasons including socio-economic, psychologic, and tumor biology, the dermatologic surgeon may still encounter large facial defects. Previously, otolaryngologists and plastic surgeons repaired these types of defects under general anesthesia. However, dermatologic surgeons can now repair most large defects in an office setting using skin flaps and local anesthesia.

While there isn't an exact size that determines the intricacy of repair, in general, a complex skin defect may be defined as one that is >50% of a cosmetic unit. Yet, defects are defined not only by their sheer size, but also by missing structures such as mucosal lining, cartilage, fat, and muscle, which are necessary for the subsurface framework.<sup>1</sup> Accordingly, small defects on the nose or eyelid that include significant cartilage or posterior lamellar components also require complex closures.

### Principles of Closure

When faced with a large repair, often there is a temptation to focus on the size, and to ignore fundamental principles of facial reconstruction. Not surprisingly, following these axioms will often facilitate closure of the surgical wound. These principles include determining if multiple layers must be replaced, locating the reservoir of skin, and maintaining both function and aesthetics.

If multiple layers are involved, the defect may require bulk or bulk-plus structure. For defects requiring bulk alone, muscle, or a fat graft may adequately fill the defect. For structural defects, calvarial bone, rib cartilage, nasal cartilage or auricular cartilage may be used to recreate the subsurface framework. These reconstructions most commonly involve the ear and nose.

Skin may be moved from a single cosmetic unit or from

multiple adjacent sites and must be mobile enough to close the defect with minimal tension. When designing a flap to close a large defect, it is essential that the major tension vector is parallel to any nearby free margins to avoid distortion of critical units such as the eyelid, nasal ala, or oral commissure. In addition to placement of the flap incision, integrity of the cosmetic unit, layered closure, and wound eversion will promote a favorable aesthetic result.

### To Wait or Not To Wait

The initial decision in closing a large defect is whether to delay the repair. This is often an appropriate strategy. Advantages include wound contraction, which closes the defect by shrinking it, as well as granulation, which improves the survival of delayed flaps and grafts. A disadvantage of delaying closure is that significant contraction may require up to 1 month, thus imposing substantial wound care challenges. Furthermore, contraction of large wounds may result in deformation of nearby structures such as the eyebrow, eyelid, nares, or mouth.

### Anesthesia

Large head and neck defects are routinely repaired using local anesthesia. The key to these repairs is the use of tumescent anesthesia (0.1% lidocaine with 1:500,000 epinephrine), which provides adequate anesthesia and excellent hemostasis. On rare occasions when patients need additional oral sedation or pain medication, 0.25mg of alprazolam (Xanax<sup>®</sup>, Pfizer) and one tablet of hydrocodone and acetaminophen (Vicodin<sup>®</sup>, Abbott) is usually sufficient. Tumescent solution is infiltrated slowly, usually requiring no more than 100mL, and reconstruction is begun after waiting 25–30 minutes. The advantages of tumescent anesthesia are its decreased risk of lidocaine toxicity, excellent hemostasis, and hydrodissection of tissue planes, thereby facilitating flap elevation.<sup>2</sup> Nerve blocks and field blocks can also be utilized in conjunction



with, or independent of, tumescent anesthesia, but because of redundant sensory nerve distribution on the head and neck, they often fail to achieve a full block when used alone.

### *Choosing the Flap*

Deciding on the flap is partly dependent on the location of the wound, the lines of relaxation, and how the flap will affect fixed structures. In general, if one has a favored “workhorse” flap, it is often wise to use this method of tissue transfer because of its geometric familiarity. Additionally, scar camouflage is an important consideration for large defects. For defects on the cheek, this can often be achieved by using a rhombic flap with its relatively short, angular lines or with a cervico-facial rotation flap whose lines are confined to the periphery of the face. A bilobed flap is another alternative with its secondary lobes mostly hidden pre- and postauricularly.<sup>3</sup>

The depth of the wound also needs to be considered. A deep cheek defect may require an island pedicle flap with substantial fat or a muscular component. In both the lip and eyelid, multiple layers must be replaced when missing in order to restore both bulk and function. Full thickness lip defects may require a Karapandzic flap or, for more lateral defects, a staged Abbe-Estlander flap.<sup>4</sup> Complex eyelid repairs may necessitate a lid sharing procedure such as the Hughes flap.

Repair of nasal defects follows the axiom of “replacing like with like.” For large nasal defects, this philosophy mandates replication of the inner lining, recreation of a subsurface framework, and restoration of proper skin thickness, texture, and color.<sup>5</sup>

For patients who have large, skin-only, tip and supratip defects, a birhombic repair or a Peng flap may suffice.<sup>6</sup> When performing large flaps with multiple incision lines and wide undermining, addition of a cartilage brace is often beneficial even when the framework is intact. This helps prevent nasal valve compromise from extensive wound contraction.

For moderately large defects involving the nasal ala or lower sidewall, the one-stage Spear flap is an elegant method,<sup>7</sup> although it often requires revision, thereby essentially converting it into a two-stage procedure. Alternatively, a staged melolabial flap provides a reasonable color match and a good vascular supply which enables detailed contouring. Traditionally, when this flap is contoured, it is defatted and inset. In selected patients with thin alar and narrow rims, the authors have shave-contoured the flap, which precisely recreates the rim.

For larger defects involving an entire nasal subunit or more, the paramedian forehead flap is often the repair of choice. Despite its complex design, it is a hardy flap, with a vascular supply based primarily on the supratrochlear artery along with branches of the infratrochlear artery.<sup>8</sup> When recreating the alar rim, it is necessary to insert cartilage struts using auricular cartilage from either the conchal bowl or the anti-helix. The paramedian forehead flap is then used for coverage. Traditionally, this flap is divided and contoured at 3 weeks. In selected patients, the authors have divided the flap at 1 week and contoured at 3 weeks, improving patient quality of life.

While it can be tempting to repair a large defect with only a skin graft, the long-term results and health consequences of a large skin graft can relegate the patient to years of disfigurement, and difficulty breathing from contraction of the graft.

### *Combinations of Flaps/Grafts*

Although it is always preferable to close a wound in one session, for large defects, delayed flaps can provide more reliable vascularization and superior long-term aesthetic results compared with skin grafting. On the scalp in particular, multiple rotation flaps in the form of a pinwheel may be needed to close a large defect.<sup>9</sup> Bilateral transposition flaps can also close a large defect without causing significant alopecia. In other locations such as the cheek or forehead, a combination of flaps and a full thickness skin graft may be needed to close a large wound. Strategically, the full thickness skin graft can be taken from the dog ear created by the flap.<sup>10</sup>

### *Tunneling Pedicle Flaps*

Though not as common in dermatologic surgery, plastic surgeons commonly use tunneled pedicle flaps for large head and neck defects. For regional repair on the forehead, a tunneled pedicle flap based on a branch of the superficial temporal artery can be raised laterally, and tunneled to cover a medial defect.<sup>11</sup> Similarly, for a large nasal root defect, a glabellar flap based on the supratrochlear artery can be easily manipulated to cover fairly sizeable defects. The drawbacks of tunneled flaps include the relatively limited distance that they can travel and the common presence of a ridge above the pedicle, which negatively affects the final esthetics.

### *Tissue Expansion*

Tissue expansion has been frequently used in the past for large areas with immobile skin such as the scalp and forehead.<sup>12</sup> This technique is effective, but significantly delays closure and can increase patient morbidity. In brief, the method involves dissection of a pocket and insertion of a silicone expander which is then filled with saline. Volume is added on a weekly basis for up to 2 months until the desired expansion is reached. The expander is removed, and the appropriate flap is performed. In addition to having to undergo an additional procedure, the expander is temporarily disfiguring, and there is a risk of infection.

### *Skin Grafts/Artificial Equivalents*

For large defects on the head and neck, skin grafts are best used in conjunction with a skin flap since, in the large majority of patients, the use of large skin grafts alone will lead to inferior cosmesis. In patients with very large defects on the scalp and no contiguous donor site for tissue transfer, a split-thickness skin graft may be indicated. For smaller facial defects, the use of artificial skin substitutes, such as Apligraf® (Organogenesis) and Integra™ (Integra Lifesciences) have been reported as effective coverage methods.<sup>13</sup> For deeper wounds, it is important to layer the

Integra™ to fill the volume deficit, and if desired, Apligraf® can be applied on top of the Integra™.

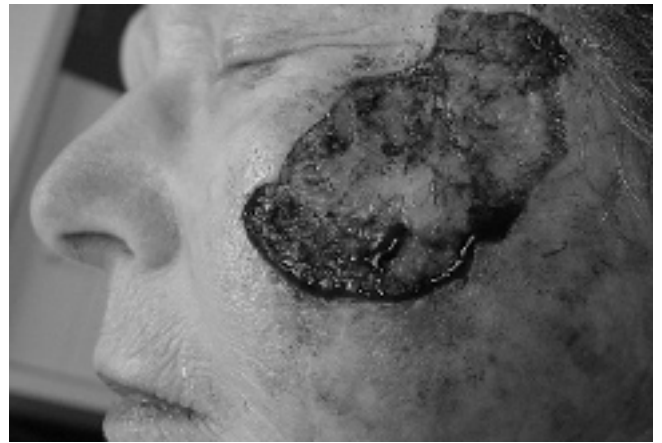
### *When To Refer*

The question of when to refer is more complicated than it appears. In addition to the size of the defect, it depends on factors such as the skill of the dermatologic surgeon, and the health of the patient. Generally, nasal defects involving the sinuses and upper nasal defects that require calvarial bone would be appropriate to refer to an otolaryngologist. Similarly, though many dermatologic surgeons repair eyelid defects, patients who have full thickness defects >50% of the lid may be best served by an oculoplastic surgeon. Extensive deep facial defects that involve multiple cosmetic subunits and have no discernible donor site may require a large regional muscle flap, such as a pectoralis flap or a free tissue transfer by either an otolaryngologist or a plastic surgeon. Full thickness lip defects, in which the repair will significantly decrease stoma size, require hospitalization. If they involve the oral cavity they may have more favorable results from an otolaryngologist or oral maxillo-facial surgeon. Finally, near total auricular defects that require rib grafts should generally be referred to a plastic or facial plastic surgeon.

### *Pearls*

A helpful technique for closing large wounds is the use of suspension sutures, also known as plication sutures. These sutures are commonly used in rhytidectomies to approximate deeper tissues and reduce wound tension. In brief, the technique involves an anchoring stitch to a stable structure such as the fascia or periosteum, and then taking a bite of tissue 1-2cm away from the initial bite, with approximation of these “edges” in a buried fashion.<sup>14</sup> Large defects may require several plication sutures. They can work well on the cheek, particularly when performing a cervico-facial rotation flap. In this situation, plication sutures can also be used to elevate the malar fat pad in order to recreate the malar eminence.

Intraoperative tissue expansion may also be of value in closing a large defect. This type of expansion can be accomplished with either towel clamps or a series of temporary nonabsorbable sutures.<sup>15</sup> Using this technique for as little as 30 minutes will lengthen enough of the collagen fibers to permit a better approximation of the skin edges. While this technique alone does not significantly aid closure of large defects, a combination of this type of expansion along with plication sutures and an appropriate flap will generally result in a satisfactory outcome. If the wound still will not close, a partial closure in many cases may be appropriate, followed by final closure in 2-3 weeks.



**Figure 1A:** A 45cm<sup>2</sup> defect on the left cheek following Mohs micrographic surgery for a Lentigo Maligna



**Figure 1B:** A rotation flap was designed. Wide undermining is necessary in order to mobilize this type of flap.



**Figure 1C:** Immediate postoperative. The flap is well perfused.





**Figure 1D:** Three months post procedure. The scars are well hidden, and because a malar suspension suture was placed, the patient does not have abnormal descent of her left malar eminence secondary to wound contraction.

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## Update on Drugs

Class	Name/Company	Approval Dates and Comments
<i>Antineoplastic Agent</i>	<b>Diclofenac Sodium 3% Gel</b> <i>Solaraze</i> <sup>®</sup> SkyePharma	The Australian Government Department of Health and Ageing Therapeutic Goods Administration approved this antineoplastic drug in November 2006 for the management of actinic keratoses.
<i>Antibacterial Agent</i>	<b>Retapamulin Ointment 1%</b> <i>Altabax</i> <sup>™</sup> GlaxoSmithKline	The US FDA issued an approvable letter in December 2006 for this topical antibacterial for the treatment of secondarily-infected traumatic lesions. This type of infection is most commonly caused by <i>Staphylococcus aureus</i> and <i>Streptococcus pyogenes</i> .
<i>Skin Filler</i>	<b>Calcium Hydroxylapatite Microspheres in Water-based Gel</b> <i>Radiesse</i> <sup>®</sup> BioForm Medical	The US FDA approved this cosmetic dermal filler in December 2006 for two indications: for the long-lasting correction of moderate-to-severe facial wrinkles and folds such as nasolabial folds, and for the long-lasting correction of lipoatrophy in people with HIV.
<i>Oncologic Agent</i>	<b>Rose Bengal Disodium 10%</b> PV-10 Provectus Pharmaceuticals	The US FDA granted Orphan Drug designation to this anti-cancer drug in January 2007 for the treatment of metastatic melanoma.
<i>Oncologic Agent</i>	<b>Taxane Potentiator</b> STA-4783 Synta Pharmaceuticals	The US FDA granted Fast Track designation in November 2006 for this oncology drug candidate for the treatment of metastatic melanoma.

### Drug News

<i>Systemic Lupus Erythematosus</i>	The initiation of dosing in pivotal Phase 3 clinical trials of belimumab (LymphoStat-B <sup>®</sup> , Human Genome Sciences/ GlaxoSmithKline) in patients with active systemic lupus erythematosus (SLE) has been announced. In each of the two Phase 3 trials, approximately 810 patients will be enrolled and randomized to 1 of 3 treatment groups (1mg/kg belimumab, 10mg/kg belimumab, or placebo). Patients will be dosed intravenously on Days 0, 14, and 28, then every 28 days for the duration of the study, and the first trial, BLISS-76, is expected to continue for 76 weeks. The data from BLISS-76 will be analyzed after 52 weeks in support of a potential Biologics License Application (BLA). The second Phase 3 trial, BLISS-52, is a 52-week study expected to begin in the first half of 2007.
<i>Antipsoriatic Agent</i>	Phase 2 data published recently in the <i>New England Journal of Medicine</i> * showed that patients with moderate-to-severe plaque psoriasis receiving subcutaneous injections of a human interleukin-12/23 monoclonal antibody (CNTO 1275, Centocor) experienced significant clearance of skin disease and significant improvements in quality of life. At week-12 of the study, 81% of patients receiving four weekly 90mg doses of this monoclonal antibody achieved at least 75% improvement in their psoriasis, as measured by the Psoriasis Area Severity Index (PASI 75), compared with 2% of patients receiving placebo. In addition, significantly more patients in each of the three additional CNTO 1275 dosing groups achieved at least a PASI 75 improvement in their psoriasis vs. patients receiving placebo. This fully human monoclonal antibody targets the cytokines interleukin-12 (IL-12) and interleukin-23 (IL-23), and is currently in Phase 3 development for the treatment of moderate-to-severe plaque psoriasis.  *Krueger GG, et al. <i>N Engl J Med</i> 356(6):580-92 (2007 Feb).

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