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Chapter 22

LEG ULCERS

Between 10 and 20 percent of patients with sickle cell disease (SCD) due to a homozygous he moglobin S (Hb S) genotype (SCD-SS) develop painful, disfiguring, and indolent leg ulcers. The ulcers usually appear between ages 10 and 50 years and are seen more frequently in males than in females. Leg ulcers are rare in individuals with SCD-SC disease, SCD-S + -thalassemia, and patients under 10 years of age, but occur in other hemolytic anemias, such as thalassemia major. In the United States, SCD is the main hemoglobinopathy that causes leg ulcers.

PATHOLOGIC MECHANISMS

The etiology of leg ulcers is unclear. In sickle cell anemia, poorly deformable red cells may cause hypoxia and infarction of distal ankle skin, which can be ameliorated by increased fetal hemoglobin (1). Trauma, infection, severe anemia, and warmer temperatures also may predispose to ulcer formation. Decreased blood flow after the ulcer has healed often results in recurrence.

CLINICAL FINDINGS

Sickle cell ulcers usually begin as small, elevated, crusting sores on the lower third of the leg, over the medial or lateral malleolus of the ankle. Occasionally, ulcers are seen over the tibia or the dorsum of the foot. They can be single or multiple. Some heal rapidly, others persist for years, and others heal only to recur in the area of scarred tissue. In the early phase, the neighboring skin appears to be healthy, but as the ulcer persists, the surrounding skin shows hyperpigmentation with loss of subcutaneous fat and hair follicles. These ulcers can be very painful and often are accompanied by reactive cellulitis and regional (inguinal) adenitis.

A general physical examination should search for other causes of leg ulcers such as varicose veins, diabetes mellitus, and collagen vascular disease. Before therapy, a radiograph of the leg is performed to rule out osteomyelitis, which is rare, even though periosteal thickening is common.

TREATMENT

The number of well controlled trials for treatment of leg ulcers is small, the number of patients in most of them is too low, and there have been almost no confirmatory studies. Methods considered to be effective in more common conditions (burns, venous stasis, and diabetic ulcers) have been used, but evidence of efficacy is often absent. In most cases, the patient's history has been used as his control in a condition notorious for unexplained remissions and relapses. Thus, most evidence is relatively weak.

There have been many proposed treatments, including topical honey or topical granulocyte mac rophage-colony stimulating factor (GMCSF), zinc oxide impregnated dressings (Unna boots), various types of natural dressings (such as lyophilized pig skin), synthetic matrices (2) that foster healing, full-thickness skin flaps attached with microsurgical techniques, parenteral erythropoietin, and intravenous antithrombin III concentrate. Localized infection is an invariant feature (3), and proposed approaches range from acetic acid wet-to-dry dressings to gentle surgical debridement to systemic antibiotics.

Anemia is, of course, a problem; most therapeutic regimens involve transfusion to raise the patient's hemoglobin conce ntration, and some more aggressive programs attempt to dilute sickle cells below some arbitrary limit, as in treatment and prevention of stroke.

There are no published trials of various types of conventional therapy, no reports that assess th

e efficacy of transfusion, and no reports that compare skin grafting with conventional therapy aside from comparisons of pretreatment and posttreatment courses in individual patients. Particularly when evaluating surgical regimens, it is important to remember that ulcers heal with bed rest alone, and that relatively prolonged bed rest is often part of postgrafting regimens.

Any treatment for a chronic condition that causes many patients to be economically disadvanta ged must be practical and costeffective. Complete bed rest for weeks may be effective, but it is not practical; moderately expensive dressings used for an outpatient might be cost-effective, but inpatient therapy probably is not (4). Issues of cost and practicality are not considered in the following review of several controlled trials, but they underlie any choice of treatment.

Most of the controlled trials were carried out by Serjeant and coworkers in Jamaica (5), where the frequency of ankle ulcers is very high and their etiology is complex. In the first trial, 29 patients received either zinc sulfate or placebo for 6 months in addition to woundcare; 13 cases in the zinc group improved, compared to 8 in the placebo group. No statistical analysis of the difference was reported. Later, topical antibiotic spray was compared to sodium chloride solution in 28 patients (6); 6 of the control patients were taking oral zinc sulfate. For ulcers of the same initial size, those treated with the topical antibiotic were 66 percent smaller ($p<0.05$) after 8 weeks.

A later trial compared Solcoseryl, Duoderm, and conventional therapy (7); patients did not toler ate Duoderm, and results with Solcoseryl were not significantly different from conventional therapy.

Perhaps the most useful but frustrating controlled trial of treatment for ankle ulcers was that of Wethers and coworkers (2). Fifty-five patients with chronic nonhealing ulcers were randomized to treatment with or without a gel composed of an arginine-glycine-aspartate (RGD) peptide (a binding site for integrins on cell surfaces) and sodium hyaluronate for cell attachment. Healing was accelerated in patients treated with the RGD peptide matrix ($p=0.0085$), and the gel was as effective in ulcers of long duration as it was in those of shorter duration. Although the study appears to have been well designed, the manufacturer of the RGD matrix for clinical use is defunct, and the compound is no longer available.

SUMMARY

Studies to prove the efficacy of treatment of leg ulcers are difficult to perform. One reason is that healing depends on blood circulation, and the cumulative time of bed rest and leg elevation is not easily monitored. In addition, the variable extent of wound debridement is difficult to quantify, and a short period of dependency could erase any gains made in the previous period. Thus, no treatments have been proven to work well or consistently. Stated differently, the "strength of evidence" that any available treatment except bed rest and wound cleansing is really effective is not good, a conclusion similar to that of a recently published comprehensive review (3).

Since the one apparently effective compound is unavailable, practice is empirical, rather than b
ased on firm evidence. Outpatient treatment
is cheaper than hospitalization and can be
achieved with intermittent clinic visits for
supervision. Some patients will be unable to
follow medical advice if they cannot stay off
their feet because of employment or domestic
duties, afford to buy dressings, or follow
instructions on how to change dressings.

In such cases, considerable ingenuity on the part of the physician or nurse may be needed. The
caregiver can provide encouragement
and understanding, which can help the patient
accept the long duration of treatment.

RECOMMENDATIONS

Ankle ulcers are painful, and the patient should be given moderately potent analgesics such as
oxycodone. Bed rest and elevation of
the leg to reduce edema are useful, though not
always practical. Wet-to-dry dressings, even
if applied only 2 or 3 times a day, can providegentle debridement; cooperation of patients
increases when they are permitted to dampen
the dressing slightly before removal, since itis a painful process. Oral zinc sulfate (200 mg3
times a day) probably does no harm if it does
not cause nausea, and may be worth using.

Ankle ulcers are always colonized with pathogenic bacteria, usually *Pseudomonas*
aeruginosa,Staphylococcus aureus,
and/or
Streptococcus
species (8), and sometimes the ulcers are
acutely infected. The infection also can besystemic. In the colonized patient, topical

antiseptics (dressings soaked with dilute acetic acid, silver sulfadiazine cream, etc.) may be helpful, but topical antibiotics invite growth of treatment-resistant strains and should be avoided. In acutely infected patients, vigorous systemic antibiotic therapy is indicated.

Periosteal thickening is usually present beneath the ulcer, but osteomyelitis is unusual. After pain and swelling have subsided, the use of Unna boots can be helpful. Patients can be taught to change the dressing themselves, and must be instructed to remove it promptly if swelling recurs. Patients need to know before a boot is first applied that a shoe may no longer fit when the boot is in place, and a loose sneaker or sandal may fit more easily.

If there is much exudate, the boot may need to be changed 2 or 3 times a week; as ulcers impr ove, weekly changes are sufficient. The ulcer size should be measured at every clinic visit; seeing the dimensions shrink can provide encouragement to the patient.
Some ulcers will not heal. Rigorous studies have not been done to assess the utility of transfusions for treating leg ulcers (see chapter 25, Transfusion, Iron Overload, and Chelation), but the ulcers seem to correlate with degree of anemia, which suggests transfusions may help. They should be considered for recalcitrant or recurrent skin ulcers if conservative therapy fails. If transfusions are used, they probably should be continued for 3 to 6 months. There is no evidence that a specified posttransfusion hemoglobin concentration or percentage of sickle cells is better than another, but a hemoglobin concentration above 10 g/dL with Hb S levels less than 50 percent can be achieved.

More complete bed rest, systemic antibiotics, transfusions, and skin grafts sometimes help. If

split thickness or pinch grafts are to be used, preoperative preparation of the ulcer bed is probably quite important. Quantitative bacterial cultures of biopsies of the bed and margin are advocated by some (9) but not all (10) surgeons as a guide to the time for surgery.

Microsurgical attachment of myocutaneous flaps may sometimes succeed when all else fails (11), but this rather heroic procedure is not always successful (12).
Because leg ulcers are less common in patients with high fetal hemoglobin (Hb F) levels, it would seem logical to try to raise Hb F concentrations.

Intravenous arginine butyrate infusions have been reported to cause rapid healing of ankle ulcers (13). Hydroxyurea is not a good choice, because it appears to cause leg ulcers in patients with myeloproliferative disease (14). Unfortunately, the effect of this drug on ankle ulcers was not recorded in the Multicenter Study of Hydroxyurea.

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