

Epidermolysis Bullosa Commands Aggressive Tx

BY KERRI WACHTER

PHILADELPHIA — When it comes to the management of epidermolysis bullosa, patient preference for bathing and dressings is important, follow-up is key to the treatment of associated anemia, and lesions suspicious for squamous cell carcinoma should undergo early biopsy and be treated aggressively, according to Dr. Dedee F. Murrell, an expert in the care of patients with this painful condition.

Dr. Murrell focused on these areas during her presentation on the management of epidermolysis bullosa (EB) at the annual meeting of the Society for Pediatric Dermatology. In Australia, she is the chair of the dermatology department at St. George Hospital in Kogarah, New South Wales, and a consultant dermatologist for EB at Sydney Children's Hospital in Randwick, New South Wales.

Dressings and Bathing

There is no consensus on how to bathe infants with EB. "There's still debate about whether you should immerse the baby completely in the bath or change the dressings limb by limb," she said. Although the limb-by-limb method may be easier to teach parents, one drawback is that the baby never learns to be comfortable with the bath setting.

"We've found it very useful in Sydney to use heated-up normal saline baths for these newborns. It makes [the water] comfortable and doesn't sting their skin when they go in the bath," she said. Some older children move on to showering, but most do not like the feeling of water splashing on their skin and prefer bathing.

"We tend to recommend saline baths for bigger patients," she noted. Patients are advised to add 1 kg of swimming pool salts to the bath water. Swimming pool salts are cheaper to use than table salt. Sometimes patients are advised to add a half cup of bleach to reduce colonization of the skin.

When their dressings are changed, it is important for patients or their caretakers to pop the EB blisters to reduce the extension of the blisters. Dr. Murrell and her colleagues usually recommend using a large-bore (such as a 19-gauge) sterile needle, which is inserted parallel to the skin surface so that it doesn't hurt the underlying skin. It's better to rupture the blister in the lowest part, so that it does not reaccumulate fluid when the patient stands. Next, press gauze over the blister to drain and collect the fluid. "Some patients prefer scissors and others even use scalpels, but I think there are [fewer accidents] with the needles," she said.

As for the optimal dressing, "I believe, personally, that the ideal dressings for EB are still to be found," said Dr. Murrell.

For now, nonstick, silicone-based dressings appear to be the best option. However, most of these require secondary dressings of variable thickness to absorb the exudate, depending on the wound. Some products are available with combined primary and secondary dressings.

Most dressings need bandages to hold

them in place. "You need special training and experience not to wrap them too tightly and cause new blistering by too much pressure at the edge of these dressings," she said. For children—especially those with recessive dystrophic EB (RDEB), whose fingers are eroded—parents need to be taught how to wrap the fingers individually. Parents also need to be taught how to lift children with EB to avoid causing more blisters.

Silver-impregnated dressings are also an option, particularly the newer ones that are silicone based. However, these cannot be used continuously for a long period of time because of the possibility of argyria.

Anemia

"It turns out that it's not just iron-deficiency anemia these patients have, but anemia of chronic disease as well," said Dr. Murrell. Patients with EB have persistently open wounds and repeated infections. As a defense mechanism, cytokines reduce the availability of iron so that infectious organisms cannot use it. Reduced iron availability, coupled with loss of iron through the skin, leads to low serum iron and altered iron metabolism. The inflammatory response in these patients also leads to blunted erythropoietin response. Cytokines, such as interferon-gamma and tumor necrosis factor-alpha, interfere with bone marrow response to erythropoietin.

"Malnutrition doesn't assist us in the management of anemia either. That's another problem these patients face," said Dr. Murrell. Patients with EB have low protein and albumin levels, and may also have low vitamin C levels. Protein has been shown in animals to lower the body's production of erythropoietin. In addition, iron deficiency can cause mucosal changes that reduce the intestine's ability to absorb iron. As a result, patients with EB need parenteral iron. Intravenous parenteral iron is preferable because intramuscular injection is painful and these patients often have low muscle mass.

Anemia treatments include combinations of oral iron supplements, blood transfusions, parenteral iron infusions, and erythropoietin. Patients taking oral iron supplements should be advised to take them between meals and without milk to improve absorption. The ferrous form is more soluble and better absorbed; however, this advantage comes at the cost of more side effects (such as constipation). The ferric form is less soluble and has fewer side effects, but leads to a slower response.

Poor compliance rates with oral iron supplements often result from dysphagia and constipation. However, poor gastrointestinal absorption and lack of bone marrow response may also contribute to poor results. Adequate vitamin C levels can improve iron absorption, she said.

Blood transfusions are reserved for patients with low hemoglobin (less than 7 g/dL). Use of transfusions tends to be restricted because of adverse events, said



This patient with recessive dystrophic EB and pseudosyndactyly did not attend regular follow-ups. She developed SCC on the right hand (above), and it had to be amputated.

Dr. Murrell. These adverse events include the potential risk of infection (for example, from hepatitis). In addition, transfusions may require time off from work for family members, and may result in psychological costs as well.

Iron transfusions had fallen out of favor because of reactions to intravenous iron-dextran and intramuscular iron-sorbitol-citric acid. However, ferric hydroxide-sucrose mixtures are safer to use. "We're now using these iron infusions many times as an alternative to blood transfusions," she said.

Iron deficiencies need to be corrected for erythropoietin to increase erythropoiesis and raise hemoglobin levels. Studies of erythropoietin that was given to improve chronic anemia in children with inflammatory arthritis have shown improvements in quality of life, energy levels, appetite, and mental functioning. However, the drug did not work without adequate iron levels.

At the EB clinic in Sydney, patients have blood work done 3 weeks prior to a visit. Physicians look at patient levels of hemoglobin, mean corpuscular volume, reticulocyte count, and soluble transferrin receptor levels. If iron levels are low, they will start the patient on oral iron and vitamin C supplements, along with nutritional support.

However, if a patient fails to respond, erythropoietin levels are checked. Iron infusions are then given every 3 months. If iron levels increase, the patient is started on erythropoietin every 2 weeks. Blood parameters are monitored every 3 months.

Squamous Cell Carcinoma in EB

SCC in patients with EB is more aggressive than other cutaneous SCCs and occurs at a much younger age, Dr. Murrell noted. "These tumors behave in a highly anaplastic way, despite looking well differentiated on pathology." SCC is the No. 1 cause of death in patients with recessive dystrophic EB, she said.

Most SCCs arise on the hands and feet. "However, [these SCCs] are often multifocal, so you can't just examine the hands and feet of these patients. SCCs

arise in wound margins at the sites of chronic blistering and scarring," Dr. Murrell said. The appearance of these lesions can be highly variable. "They may look hyperkeratotic and exophytic, but sometimes they just look like ulcers that haven't been healing," she said. Typically, several biopsies are necessary to exclude SCC.

SCCs in patients with EB appear to be associated with chronic wounds. "One of the theories is that there are mutations arising during wound repair [that] are not being recognized and being fixed," said Dr. Murrell.

"The early recognition of SCC is really important. In my mind, it's like early recognition of melanoma," she said.

Dr. Murrell and her colleagues have been following 16 RDEB patients since 1999. They perform biopsies on any nodules or ulcers that persist for more than 3 months, or any nodules that become enlarged or are painful. Photographic monitoring provides documentation of erosion size and location. This is very helpful in identifying and performing biopsies on lesions that persist.

One of the keys to this approach is patient participation. Dr. Murrell told of a 20-year-old patient who did not regularly attend these sessions, and ultimately had to have her hand amputated. In contrast, a 60-year-old patient has had more than 50 early SCC excisions and is still doing well. "She jumps at getting the biopsies done as soon as she realizes there is anything unusual or untoward about any of her wounds," said Dr. Murrell.

Patients with EB need vigilant monitoring for SCCs. Treating physicians should have a low threshold for biopsy. If an SCC is identified, a wide excision should be performed, said Dr. Murrell.

In terms of treatment, Mohs surgery has been used for SCCs in patients with RDEB. However, "I'd be hesitant to use that because the margins are not very big," she said.

Retinoids have been proved to reduce SCCs in immunosuppressed patients. "We use them a lot in Australia in elderly people with multiple SCCs," said Dr. Murrell. In particular, isotretinoin and acitretin are both well tolerated.

One area of active research is the use of epidermal growth factor receptor (EGFR) inhibitors. EGFR is strongly expressed in metastatic SCCs of the skin. Cetuximab is indicated in the United States for the treatment of locally or regionally advanced SCC of the head and neck in combination with radiation therapy, and in recurrent or metastatic SCC of the head and neck that progresses after platinum-based therapy.

Dr. Murrell reported that she has received financial support from Mölnlycke Health Care, which makes wound dressings. ■