EPEC-O

Education in **P**alliative and **E**nd-of-life **C**are - **O**ncology

Participant's Handbook

Module 3q:
Symptoms – Skin

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Case*

P.L. is a 74-year-old woman who comes to the office complaining of a 'rash' on her right chest. She says it has been there for 'a few weeks' and it is only modestly painful (2-3/10 in intensity). What bothers her most is that it is oozing. This soils her clothing. In the past few days, there has been some bleeding which made her seek medical attention. Her past history is significant for a stage II adenocarcinoma of the breast (ER positive), treated with mastectomy and adjuvant tamoxifen 4 years ago. She did not undergo adjuvant radiation.

Examination shows a reddened area with an irregular surface covered by a disposable diaper. The dressing is saturated with a serosanguineous discharge. When the dressing is removed, the smell is overpowering. Biopsy shows adenocarcinoma.

* This case is not on an EPEC-O Curriculum trigger tape.

Introduction

Basic principles that underlie the management of skin problems in cancer care include first, classification of the skin problem as acute or chronic; second, determination of whether the skin problem is likely to heal or not.[1] These basic principles can be applied to a variety of specific situations: chemotherapy extravasation, radiation damage to the skin, decubitus ulcers, and malignant wound management. These same principles can also be applied to related situations.

Other symptoms and conditions are frequently associated with skin problems. The incidence of depression is high. Pain is also important. In addition, there is an inordinate burden of anxiety that accompanies the care of skin problems, particularly in anticipation of debridement and dressing changes due to the pain and distress that these procedures can cause.

Pathophysiology

The skin is an organ system with highly developed physiology. It has essential functions in the regulation of homeostasis and immunity. For example, a skin wound permits infectious organisms to bypass some of the essential immunological barrier functions of intact skin.

Second, the skin is highly innervated. Teleologically, such innervation helps the body sense the environment and avoid injury. However, if the skin is involved in a pathological process, the innervation may lead to profound symptoms and be a source of considerable suffering. In fact, many of the pathological processes that can involve the skin lead to sensitization of the cutaneous nerves. Such sensitization leads to recruitment of additional neurons and increased neuronal firing of each involved neuron. Though opioid receptors are not present in normal skin, within minutes to hours of inflammation, opioid receptors are present in peripheral sensory nerves.[2] In other words, there is a sound

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pathophysiological basis for a patient's experience of profound pain from the skin and a foundation for its rational treatment. The personal awareness of the symptom will greatly exceed that of a comparable injury to an internal organ that has minimal innervation.

Third, the skin is the most visible organ. Changes in appearance may have profound consequences for the person who has them. One of the most common examples in oncology is hair loss. From a purely medical model, hair loss is a trivial, reversible consequence of some types of chemotherapy. However, for the patient, its impact may be so profound as to lead the patient to avoid life-saving therapy in order to maintain an intact sense of body image.

Some would say that the psychosocial role of the skin is the most important. People form opinions of one another based initially on sight, then through conversation. Disfigurement can be extremely distressing. With contemporary emphasis on how we look, it is no surprise that disfiguring skin conditions can lead to profound psychological, social, and spiritual distress. In addition, it can affect the care provided. Patients who look or smell bad may receive less care and perceive more distance because their caregivers do not want to be with them or to touch them.

Skin injury and symptoms can be divided into two broad categories: acute and chronic. Acute injuries to skin, such as operations or radiation, are associated with an acute pathophysiological response. Products of inflammation, chemotactic factors, hyperemia, and swelling are all initiated. This leads to increased pain and an increased pain response to ordinarily non-painful stimuli. In contrast, chronic injury and symptoms may not be associated with the same pathophysiological responses. In fact, chemotaxis and increased blood supply may be absent from chronic wounds and symptoms. Pain may or may not be associated with chronic wounds.

Wounds tend to fall into distinct categories, each with its own pathophysiology. The categories include: chemotherapy extravasation, radiation injury, decubitus ulcers, and malignant wounds.

Chemotherapy extravasation

Chemotherapy extravasation, particularly with a vesicant, is an example of an acute wound.[3] An acute wound produces skin damage of varying degrees. The result of the wound is an acute inflammatory response. The products of inflammation lead to several predictable sequelae. The area becomes red because of increased blood flow. The capillaries leak large amounts of fluid that lead to swelling. Direct stimulation of nerve endings, as well as recruitment and sensitization of those nerve endings, leads to pain.

If the wound is severe, significant cell death can occur. This leads to tissue necrosis and sloughing. The result is an open wound. The time for healing relates to the healthiness of unaffected skin and the amount of tissue that has died.

Radiation injury

Skin damage due to radiation therapy is another example of an acute wound.[4] The products of inflammation cause erythema, swelling, and pain. Cell death leads to peeling skin.

Decubitus ulcers

Decubitus ulcers are frequently encountered in patients with cancer, particularly those debilitated who are by their illness or by treatment.[5,6] Intrinsic risk factors for the development of decubitus ulcers are limited mobility, medical conditions that reduce tissue oxygenation, age-related changes in skin, and poor nutrition.

Closure of microarterioles secondary to pressure leads to ischemia with pressure points at particular risk for the development of decubitus ulcers.[5,7] Examples are heels, sacrum, and elbows. Skin can withstand 30-60 minutes of poor perfusion but not longer. Fat normally provides a cushion and more evenly distributes pressure. Therefore, thin and cachectic patients lack a fundamental protective mechanism. Shear, friction, and moisture compound the skin at risk.

Malignant wounds

Malignant wounds are an example of a chronic wound. Malignancies may involve the skin either as a primary site or as metastases.[8] Malignant cutaneous wounds are most commonly associated with cancer of the breast and lung.[2] A malignant wound is frequently painful because of the local tissue reaction and the products of inflammation.[4] However, due to neovascularization and subsequent necrosis as the tumor outgrows its blood supply, there may be significant bleeding. In addition, necrosis may lead to infection, particularly with anaerobic and fungal species. The most common organisms associated with these lesions are proteus, klebsiella, and pseudomonas.[4] These infections can be painful and can also cause foul odors.

Lymphedema, peripheral edema

Lymphedema results after, for instance, full axillary lymph node dissection as part of breast cancer treatment and in some advanced hematologic malignancies. Peripheral edema occurs in numerous advanced cancer conditions that result in, for instance, paralysis, ascites, hypoalbuminemia or congestive heart failure.

Assessment

Chemotherapy extravasation

Assessment begins with determining what kind of drug has leaked into tissues.[3,9] Chemotherapy drugs fall into 3 classes: vesicant, irritant, and those that do not cause

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tissue damage. A vesicant (examples are mitomycine-c, doxorubicin, vinblastine, vincristine, vinorelbine) is capable of causing severe tissue damage and necrosis if the drug is extravasated in the surrounding tissue. Irritants such as carboplatin or etoposide are irritants in that they lead to an inflammatory reaction, but do not cause cell death directly. These drugs are capable of producing venous pain at the injection site or along the vein. Finally, there are a group of drugs such as fluorouracil, which are benign and do not cause problems other than those from local volume effects.

Second, the extent of extravasation should be assessed. How much volume of drug was extravasated? What was the rate of flow and how much time elapsed since the extravasation began? What is the mechanism of tissue damage from the extravasated agent? These factors can help to estimate the amount of damage that might have been caused.

Third, the involved anatomy should be assessed. What tissues are likely to be involved? Is this a small amount of an irritant in the subcutaneous tissues? Or, is this a large extravasation that is likely to involve underlying muscles, tendons, and nerves? Tendons and nerves are the most susceptible to irreparable damage. They are so critical because of the issue of function—if these structures are irreparably damaged, chronic pain and disability may occur distal to the injury. For example, if an extravasation of doxorubicin in the arm is not assessed and treated swiftly, muscles, tendons, and nerves will be damaged. As a result, the function of the hand and forearm will be compromised. If nerves are damaged, there will not be feeling or movement.

Serious extravasations of irritants or vesicants may result in a necrotic wound. An assessment should be made as to whether a surgical consultation is required. This is indicated for any volume of doxorubicin more than a few cc. For smaller volumes of less dangerous drugs, a watch and wait strategy may be all that need be done.

Radiation

Determine whether exacerbating factors were involved. Creams, lotions, and bandages can increase the effective dose of radiation to the skin and increase tissue damage. For example, a hydrocolloid dressing placed on the skin will raise the dose of radiation to the skin. Systemic drugs can also cause sensitization. This may be intended, as with chemotherapy used as a sensitizer, or unintended. The radiation oncologist should be aware of all drugs, including alternative or complementary therapies, that a patient is taking.

For each dose and fractionation schedule, there is an expected course of skin damage. For example, the effective dose to the skin is low with gamma radiation applied to deep structures. Damage to the skin is unlikely to be more significant than a bad sunburn. In general, skin effects are not seen until 1-2 weeks after therapy has begun. The damage can increase during the remainder of therapy and not begin to resolve until several weeks after therapy is completed.

A critical issue is at which anatomical level the dose of radiation is concentrated: at the surface or deep to the skin. In general, radiation therapy will not a have high impact on the skin unless special techniques are used to focus radiation to skin. The larger the fraction size, the more effect that dose has on any tissue (skin or deep tissues).

Decubitus ulcers

A widely used staging system for decubitus ulcers is helpful in determining management.[5,7] Ulcers progress in a step-wise fashion. If ulcers are caught early and appropriate prevention and treatment are initiated, the ulcer will not progress.

- Stage I: The heralding lesion of skin ulceration is non-blanchable erythema.

- Stage II: Partial-thickness skin loss involving epidermis, dermis, or both. The ulcer is superficial and looks like an abrasion, shallow crater, or blister.

- Stage III: Full thickness skin loss involving subcutaneous tissue. The ulcer may extend down to, but not through, the underlying fascia. The ulcer looks like a deep crater, with or without undermining of adjacent tissue.

- Stage IV: The ulcer is deep enough to include necrosis and damage to underlying muscle, bone, and/or other supporting structures such as the tendon or joint capsule. Undermining of adjacent skin and sinus tracts may also be present.

The treatment approach rests on an assessment of whether the overall goal is to heal the wound or not. For many patients with advanced cancer and short prognosis, it is unrealistic to expect the wound to heal. However, for some patients, healing is possible.

If the goal is to heal, then debridement, as outlined earlier, and the application of dressings that promote healing are appropriate.

If the wound will not heal, then the primary goals are pain control and comfort. In addition, steps should be taken to prevent worsening

Malignant wounds

As for other chronic wounds, a fundamental decision needs to be made about whether the wound will heal or not. In addition, assess for infection. Malignant wounds carry a high risk of superficial infection.[10] Odor is frequently the first sign of an anaerobic infection. There may be purulent exudates.

Lymphedema, peripheral edema

Propensity for lymphedema should be considered so that preventive measures can be taken. Edema should be assessed for its impact. It may cause body image problems, discomfort, poor wound healing if wounds are in the same area, and may result in breakdown of skin and subsequent infection.

Management

The first management principle that underlies the approach to skin symptoms is prevention.[3,5,6,8] Some skin symptoms can be prevented. For example, careful attention to planning and technique will prevent chemotherapy extravasation and radiation injuries. Attention to pressure points and adequate skin protection will prevent decubitus ulcers. Time spent in prevention will avoid the time, expense, and suffering associated with these preventable skin injuries.

Management will be influenced by whether or not the wound or symptom is likely to resolve and heal. For wounds that will heal, management will focus on relieving associated symptoms and promoting healing. For situations that will not resolve, management will focus only on relieving associated symptoms.

Chemotherapy extravasation

The first step of management is to contain the damage.[9] The infusion should be stopped as soon as there is even a suspicion of extravasation. Any remaining drug should be withdrawn from the line. Tissue damage secondary to extravasation of a vesicant occurs from one of two major mechanisms. Drugs that bind to cellular DNA (eg doxorubicin) cause local cell death. When the drug is released into the surrounding tissue, the drug remains active and causes damage to adjacent cells. Avoid compress and application of DMSO; hyaluronidase infiltration is recommended for this type of injury.[11,12,13] When tissue damage is not related to binding of cellular DNA (eg vinca alkaloids), local tissue damage is more easily neutralized. Heat, rather than cold, should be applied.[14] Dexrazoxane may be useful as a partial antidote based on some case reports.[15] Once damage is limited and urgent approaches performed, watchful waiting is all that can be done to see what damage will result. Institutional guidelines and policies regarding the use of antidotes through the infiltrated line or subcutaneously around the site of infiltration are generally available. A table of these appears in most comprehensive textbooks and should be available, along with a standard protocol, in sites where chemotherapy is administered.

For necrotic tissue, debridement is required. Normal healing cannot occur until dead tissue is removed. The goal is to debride to clean margins. Before debriding a wound, it is important to assess the viability and perfusion of surrounding tissues. It may be appropriate to delay debridement and consider a maneuver such as hyperbaric oxygen therapy to enhance vascularization prior to debridement.[16]

There are a variety of ways that debridement can be accomplished. Surgical debridement is the fastest, most effective way to remove necrotic tissue. It requires a skilled surgeon and adequate analgesia. Particularly in the case of extravasation of vesicants, it is possible to have normal tissue on top occluding and containing necrotic tissue below.

Debridement gels, available with or without enzymes, encourage autolytic or enzymatic debridement. These are appropriate for wounds when surgery is either not indicated or

was incomplete. For example, a doxorubicin extravasation with extensive necrosis may need surgery first. However, there may subsequently be tissue slough and exudate. These can be managed with the debridement gels. Remember that damage to normal tissues can occur if the debridement gel is left in too long. Occlusive dressings with hydrocolloid dressings promote autolysis by maintaining a moist environment for autolytic enzymes to work.

Mechanical debridement can be utilized using saline wet to dry dressings, although it is not recommended. This is accomplished by placing gauze wetted with saline on the wound. After the gauze has dried, it is peeled off. Not surprisingly, this is usually painful. In addition, it does not promote healing because it also peels off the new epithelial cells as part of healthy granulation tissue. In other words, saline wet-to-dry dressings should be used rarely, if at all.

Pain control is a critical component of debridement and should be managed aggressively. Appropriate wound analgesia is likely to include a topical anesthetic and/or infiltration of surrounding tissues with a local anesthetic. For example, lidocaine gel or spray can be applied topically, as well as infused locally. If lidocaine is infused, epinephrine can be used to staunch bleeding and limit diffusion away from the wound. Liquid morphine can be mixed (in a 1:1 concentration, 1mg morphine/1ml gel) with gel (or other aqueous based cream or gel) for local pain control.[17,18]

EMLA cream may be used, although it is an 'off-label' indication in the US. It takes an hour to start working and an application provides local anesthesia for 4 hours. It can be placed under a dressing. There is no evidence that it retards the healing process. Benzocaine is contraindicated because it is an ester and a topical sensitizer for hypersensitivity reactions.

Cleansers may be used to clear away slough, exudate, and debris. In choosing a cleanser, a useful rule-of-thumb is: do not put anything into the wound you wouldn't put into your eye. Normal saline is by far the preferred cleanser. Pressure used to clean the wound should never exceed 15 pounds per square inch as it damages new epithelial cells. A 60 cc syringe filled with normal saline connected to a 19-20 gauge angiocath can be used.

Cleansers that are cytotoxic to granulation tissue must not be used to clean an open wound. This includes cleansers designed to clean normal skin, eg, hydrogen peroxide, povidone.

Our understanding of wound healing has changed. All living tissues require moisture for transport of oxygen and nutrients. By contrast, a dry environment is conducive to necrosis and eschar, not to healing. A moist wound environment promotes the migration of fibroblasts and epithelial cells. Many growth factors present in a serous exudate speed healing.

In addition to a moist environment, the bacterial burden needs to be removed as it will delay wound healing. Purulent exudates or erythema and infection of surrounding tissues should be sought. If the infection appears to be superficial, cleansing and application of

topical antibiotics may be sufficient. However, if there is evidence of tissue infection, or if wound healing is delayed, the use of systemic antibiotics should be considered.

There are 6 classes of dressings. They are distinguished by the wear time and whether they donate or remove fluid in order to maintain an ideal moist interactive wound healing environment. A dry wound needs to have moisture given to it through a hypotonic gel (donates water). If there is a lot of wet exudate, a hypertonic gel or foam should be used to remove water from the wound.

1. Foams: Most absorptive. Used under a covering dressing.

2. Alginates (sea weed): Works to desiccate an overly wet wound. Prevents maceration of surrounding skin from excess fluid. Hemostatic, may reduce risk of infection.

3. Hydrogels: Used for wounds with larger volumes of exudates.

4. Hydrocolloids: Self-adhesive. Promote autolysis, angiogenesis, and granulation. Remain in place for 5-7 days. Often used to 'seal' a wound that is otherwise clean in order to promote healing. Can also be used to seal an underlying dressing in order to maintain a moist environment in which the wound can heal. However, it is important not to use an occlusive dressing if there is a substantial risk of infection.

5. Thin films.

6. Cotton gauze: Used to cover the primary dressing. Rarely the appropriate dressing for a significant skin wound.

To reduce the risk of maceration, the surrounding skin may need to be protected.

Radiation

Radiation damage to the skin should be treated using principles for acute wound care. Cytotoxic agents that will retard healing should be avoided. If the skin integrity is breached, a moist environment should be maintained. Infections should be treated and pain appropriately managed.

Decubitus ulcers

Prevention of ulcers is essential.[5,7] Skin should be protected from friction, moisture, and shear. High-risk areas should have either thin film or hydrocolloid dressings applied. Skin also needs to be protected from pressure. Patients need either to be turned regularly or a pressure-reducing surface should be used.

There are 3 groups of support surfaces that have demonstrated efficacy:

- Air or water mattress overlays are ideal for most patients to prevent decubiti. Examples of patients who would benefit from their use include any patient who is bed-bound, has limited mobility, or is cachectic.

- Low-air-loss beds are usually used for patients who are at high-risk, or who have developed ulcers where the goal is to prevent worsening and/or promote healing.

- Air-fluidized beds are reserved for patients who need maximum pressure reduction and pressure relief. However, patients frequently describe them as overly confining (even 'coffin-like') and they are very expensive.

Simple foam pads are often ineffective. If they are used, they may need to be layered. If a hand is placed under the pads, there should be at least 1 inch of non-compressed foam between the hand and the patient for them to be effective.

Never use round cushions commonly called donuts. They occlude blood flow and do not prevent ulcers.

Patients need to be assessed professionally for the use of special pressure reducing cushions for wheelchairs and the like.

An important secondary gain of the appropriate use of skin protection and pressure reduction/relief may be pain relief.

Malignant wounds

The management principles and dressing choices are the same as for decubitus ulcers. However, malignant wounds bring up a few additional areas that deserve comment. Antineoplastic treatments may offer significant palliation of the symptoms from a malignant wound. Radiation therapy may decrease bleeding, pain, and exudate. Chemotherapy or hormonal therapy may lead to wound healing in patients with responsive disease.

If there is superficial infection, topical treatment with metronidazole or silver sulfadiazine may be sufficient. However, if there is evidence of deeper tissue infection, systemic metronidazole should be used. If the wound is non-healing, topical agents such as povidone that are cytotoxic to bacteria can be used. Povidone will help keep the wound clean although some patients find it irritating and painful. Because of its cytotoxic effect on granulation tissue, povidone should not be used for wounds that are expected to heal.

In addition to managing infection, there are other approaches to the management of odors. Odor absorbers can be used in the room. Kitty litter or activated charcoal can be placed on a cookie tray underneath the bed. In addition, a secondary covering dressing that contains charcoal or a disposable diaper can be used to cover a particularly odorous wound. Additional approaches include putting a burning flame (such as a candle) in the room in an attempt to combust the chemicals causing the odor. One can also introduce a competing odor. The simplest are bowls of vinegar, vanilla, or coffee. Fragrances and perfumes are often poorly tolerated by patients and should be avoided.

Pain can be managed with systemic administration of analgesics or with local analgesics or anesthetics. A continuous, low-dose, subcutaneous infusion of lidocaine has been advocated for particularly painful superficial lesions.

Exudates from malignant wounds can be substantial. Absorbent foam can be used to minimize the frequency of dressing changes and maximize absorption. The overall goal is to prevent the exudate from macerating other normal tissues or dripping off the patient onto clothes and bedclothes. This serves as an infection control measure and achieves a cosmetic goal. A gauze pad is typically placed on top of the absorbent foam.

The alginate dressings have a role in managing a wound that has an exudate and/or is bleeding since these dressings are hemostatic, control infection, and are absorptive. They do not have to be pulled off; they can be washed off in the shower.

Bleeding is frequently an issue with malignant wounds as the surface of a malignancy may be friable and predisposed to bleeding. It may present as either oozing (microvascular fragmentation), vascular disruption from necrosis, or sloughing leading to 'a bleeder.' Any dressing that comes into contact with the surface may adhere and tear the surface when it is pulled off. The saline wet-to-dry dressing is an example as previously discussed. This situation can be prevented by using a mesh synthetic polymer with a non-stick, non-absorbent dressing. This should be cleaned off once a week with an absorbent dressing placed over it. The alginates are hemostatic and can be useful. Topical thromboplastin can also be used; a low dose, i.e., 100 units/ml is as good as higher doses and is less expensive. Antifibrinolytics, such as topical aminocaproic acid, are sometimes used, although their role is not clear since fibrinolysis is not a major mechanism in wound bleeding. Silver nitrate or cautery can be used for frank bleeding. Radiation therapy is very effective for control of local bleeding.

Lymphedema, peripheral edema

Lymphedema prevention is more effective than management after it has occurred. Prevention and management of lymphedema include elevation of the involved limb, physical therapy movements, massage, and compression bandages. In a referral center, lymphedema clinics often exist and usually provide optimal care, especially as the cancer advances and lymphedema management may become a major focus of attention. Management of peripheral edema from other causes may include keeping the patient's fluid balance on the negative side. Although some have reasoned that reversal of hypoalbuminemia might help, there is no evidence that albumin or fresh frozen plasma infusions result in benefit, since the newly infused protein also extravasates rather than providing the desired osmotic gradient.

Key take-home points

Skin

1. Keep skin clean and dry.

2. Cover areas where prolonged urine or stool contact may occur.

3. Cover intact pressure points with thin hydrocolloid dressings.

4. Use appropriate pressure-reducing bed overlays to optimize weight distribution, reduce the risk of pressure ulcer development, and minimize contact pain.

5. Treat superficial infections with topical metronidazole or silver sulfadiazine.

6. Manage odors by using kitty litter or other deodorizers.

Pearls

1. Prevention is the best treatment for skin ulcers.

2. The skin is highly innervated. Consider topical opioids to treat the pain associated with open wounds.

3. A moist environment promotes healing.

Pitfalls

1. Donuts on wheelchair seats make things worse, not better.

2. Wet-to-dry dressings do not promote healing.

Summary

Basic principles that underlie the management of skin problems in cancer care include first, classification of the skin problem as acute or chronic; second, determination of whether the skin problem is likely to heal or not. These basic principles can be applied to a variety of specific situations: chemotherapy extravasation, radiation damage to the skin, decubitus ulcers, and malignant wound management. As in other symptoms, clinicians can use comprehensive assessment and pathophysiology-based therapy to treat the cause and improve the cancer experience

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The effect of inflammation, induced by unilateral intraplantar injection of Freund's adjuvant, on opioid receptors transported in the sciatic nerve and on opioid receptors present in the paw of the rat was studied by means of in vitro receptor autoradiography using [125I]beta-endorphin (human) as ligand. In the absence of inflammation, human beta-endorphin binding sites accumulated proximally and distally to a ligature placed on the sciatic nerve in a time-dependent manner, indicating bidirectional axonal transport. Some human beta-endorphin binding was also visible in non-inflamed paw tissue. Inflammation of the paw tissue massively increased human beta-endorphin binding on both sides of the sciatic nerve ligature and in the ipsilateral paw tissue. In inflamed paw tissue, beta-endorphin binding accumulated in the cutaneous nerve fibers as well as in the immune cells infiltrating the surrounding tissue. In the sciatic nerve and paw tissue, beta-endorphin binding was displaced by (D-Ala2, N-methyl-Phe4, Gly-

ol5)enkephalin and (D-Pen2, D-Pen5)enkephalin, selective mu- and delta-opioid receptor agonists, respectively, and by the universal opioid antagonist naloxone, but not by U-50,488H, a k-selective receptor agonist. Taken together, these data provide neuroanatomical evidence for local inflammation-induced enhanced axonal transport of opioid receptors in rat sciatic nerve and accumulation in paw tissue.

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Extravasation of chemotherapeutic vesicant agents can result in significant tissue damage, alteration in limb function, and pain. Quality of life for long-term survivors can be severely impacted by negative sequelae from vesicant extravasation. Currently, there is no known preventive therapy. Early detection and intervention are paramount to halt tissue damage and reduce the chance of permanent disability or disfigurement. This article provides an overview of known chemotherapeutic vesicants (mechlorethamine, mitomycin-C, doxorubicin, daunomycin, vincristine and vinblastine), associated theories of tissue destruction, assessment techniques for peripheral intravenous sites, vascular access devices and central venous lines, current treatment strategies, and investigational therapies. A brief discussion of the legal implications of extravasation injuries and recommended key points for medical record documentation are included.

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Bed-bound patients with pressure ulcers are almost twice as likely to die as are those without pressure ulcers. If pressure ulcers are treated with a comprehensive regimen upon early recognition, nearly all stage IV ulcers can be avoided. Furthermore, such a regimen can significantly reduce the comorbidities, mortalities, and costs of treatments resulting from stage IV ulcers. The costs of treatments for comorbidities after the ulcer progresses to stage IV far outweigh the costs for early treatment of the ulcer before it progresses beyond the early stages. We describe herein the 4 stages of pressure ulcers, as well as the pathogeneses, costs, and complications associated with these wounds. A comprehensive 12-step detailed protocol for treatment of pressure ulcers is described; this includes recognizing that every patient with limited mobility is at risk for developing a sacral, ischial, trochanteric, or heel ulcer; daily assessment of the skin; objective measurement of every wound; immediate initiation of a treatment protocol; mechanical debridement of all nonviable tissue; establishment of a moist wound-healing environment; nutritional supplementation for malnourished patients; pressure relief for the wound; elimination of drainage and cellulitus; biological therapy for patients whose wounds fail to respond to more traditional therapies; physical therapy; and palliative care. Availability of the described treatment modalities, in combination with early recognition and regular monitoring, ensures rapid healing and minimizes morbidity, mortality, and costs.

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Prevention remains the best defense in maintaining skin integrity. Daily skin inspection, gentle cleaning, cleansing after episodes of incontinence, moisturizer use, containment of drainage, and minimization of contributing factors are essential steps in caring for patients who are at risk for or who actually develop wounds. Proper techniques for positioning can be taught to the patient and the caregiver. Support mattresses and cushions may be required to prevent or treat skin breakdown. Mobility training and strengthening can make a difference in the successful treatment of wounds. Adequate nutrition is essential for healing and plays a pivotal role in the success or failure of the treatment plan.

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Although often overlooked, topical antibiotic agents play an important role in dermatology. Their many uses include prophylaxis against cutaneous infections, treatment of minor wounds and infections, and elimination of nasal carriage of Staphylococcus aureus. For these indications, they are advantageous over their systemic counterparts because they deliver a higher concentration of medication directly to the desired area and are less frequently implicated in causing bacterial resistance. The ideal topical antibiotic has a broad spectrum of activity, has persistent antibacterial effects, and has minimal toxicity or incidence of allergy.

[11]   Disa JJ, Chang RR, Mucci SJ, Goldberg NH. Prevention of adriamycin-induced full-thickness skin loss using hyaluronidase infiltration. *Plast Reconstr Surg*. 1998;101(2):370-374. PMID: 9462769.

Full-thickness skin ulceration after extravasation of the commonly used vesicant chemotherapeutic agent doxorubicin hydrochloride (Adriamycin) is a significant source of morbidity in cancer patients. Controversy exists regarding the appropriate management of this extravasation injury. Current therapy includes local hypothermia, local clysis with hyaluronidase, and surgical excision of the involved tissue. Experimental data supporting local clysis with hyaluronidase are limited despite its current use clinically. The purpose of this study was to determine the efficacy of local infiltration with heparin sodium, hyaluronidase, and saline in the prevention of extravasation ulcers in a rat model. One hundred fifty male Sprague-Dawley rats (Upjohn, Milan, Italy) weighing 240 to 260 g, anesthetized with sodium pentobarbital, were used in this study. One hundred thirty rats received a 0.3-ml subcutaneous flank injection of doxorubicin (1.5 mg/ml) followed 15 minutes later by local infiltration with saline (n = 10), 25 to 100 units of heparin (n = 30), or 2.5 to 10.0 units of hyaluronidase (n = 90). Control animals received either subcutaneous doxorubicin (n = 10) or subcutaneous saline alone (n = 10). Volumes of the infiltration solution were less than 1 ml in all groups. All animals were sacrificed at 4 weeks; presence and size of ulcers at the injection site were quantified. Statistical analysis was performed using the two-sided Fisher's exact test and Student's t test. Control rats injected with saline alone did not develop ulceration in any case. All rats injected with doxorubicin alone developed ulcers with an average size of 33 mm2. Heparin infiltration decreased ulcer rate by 20 to 40 percent and decreased ulcer size by up to 67 percent. Local infiltration with hyaluronidase decreased ulcer rate by 50 to 60 percent ($p < 0.05$, two-sided Fisher's exact test) and decreased ulcer size by up to 50 percent ($p < 0.05$, Student's t test). In this rat extravasation injury model, local infiltration with saline, heparin, or hyaluronidase decreased ulcer size after doxorubicin extravasation. This effect may be secondary to dilution of the extravasant. Additionally, local infiltration with hyaluronidase decreased ulcer rate by at least 50 percent. The mechanism of this phenomenon presumably relates to the ability of hyaluronidase to temporarily decrease the viscosity of the hyaluronic acid component of ground substance, thus allowing greater diffusion of doxorubicin into the surrounding tissue and therefore decreasing its local concentration.

[12] Bertelli G, Gozza A, Forno GB, Vidili MG, Silvestro S, Venturini M, Del Mastro L, Garrone O, Rosso R, Dini D. Topical dimethylsulfoxide for the prevention of soft tissue injury after extravasation of vesicant cytotoxic drugs: a prospective clinical study. *J Clin Oncol*. 1995;13(11):2851-2855. PMID: 7595748.

PURPOSE: To evaluate the activity and tolerability of dimethylsulfoxide (DMSO) in the prevention of soft tissue toxicity after extravasation of cytotoxic drugs. PATIENTS AND METHODS: From June 1991 to December 1994, all patients who had an extravasation during intravenous (IV) infusion of cytotoxic drugs in our institution were considered for an open, prospective study of preventive treatment with 99% DMSO, applied topically on the extravasation site every 8 hours for 7 days. Intermittent local cooling (for 1 hour three times daily) on the first 3 days was also used. RESULTS: One hundred forty-four patients with extravasations of doxorubicin (n = 11), epirubicin (n = 46), mitomycin (n = 5), mitoxantrone (n = 13), cisplatin (n = 44), carboplatin (n = 6), ifosfamide (n = 14), and fluorouracil (n = 5) entered the study; 127 were assessable. Only one patient suffered an ulceration. The treatment was well tolerated, with mild local burning and a characteristic breath odor being the only side effects of DMSO application, even in cases in which treatment continued for up to 6 weeks to obtain remission of the symptoms of extravasation. CONCLUSION: Topical DMSO is an effective and safe antidote that may be used with local cooling after extravasations of vesicant drugs other than those drugs for which standard interventions are defined.

[13] Bertelli G, Dini D, Forno GB, Gozza A, Silvestro S, Venturini M, Rosso R, Pronzato P. Hyaluronidase as an antidote to extravasation of Vinca alkaloids: clinical results. *J Cancer Res Clin Oncol*. 1994;120(8):505-506. PMID: 8207052.

Skin necrosis is a recognized potential consequence of an inadvertent extravasation of Vinca alkaloids in the surrounding tissues during i.v. administration. Experimental studies suggest that hyaluronidase, an enzyme that degrades hyaluronic acid and improves the absorption of locally injected drugs, can reduce the risk of progressing to skin necrosis. On this basis, we used this enzyme as a local treatment after extravasations of Vinca alkaloids in seven patients. No patient suffered from subsequent skin necrosis. To the best of our knowledge, this is the first clinical report confirming the positive findings of experimental studies on the effectiveness of this antidote.

[14] Pathophysiology: Tissue damage secondary to drug infiltration damage occurs from one of two major mechanisms. Cancer chemotherapy guidelines and recommendations for practice (second edition). Rudolph & Larson, 1987;35-41.

[15] Bos AM, van der Graaf WT, Willemse PH. A new conservative approach to extravasation of anthracyclines with dimethylsulfoxide and dexrazoxane. *Acta Oncol.* 2001;40(4):541-542. PMID: 11504316.

[16] Monstrey SJ, Mullick P, Narayanan K, Ramasastry SS. Hyperbaric oxygen therapy and free radical production: an experimental study in doxorubicin (Adriamycin) extravasation injuries. *Ann Plast Surg*. 1997;38(2):163-168. PMID: 9043586.

The role of hyperbaric oxygen (HBO) therapy in free radical-mediated tissue injury is not clear. HBO has been shown to enhance the antioxidative defense mechanisms in some animal studies, but HBO has also been reported to increase the production of oxygen free radicals. To investigate this controversy, we studied the effect of HBO in a doxorubicin (Adriamycin) extravasation model, because the cytotoxic activity of doxorubicin is partly related to its quinone structure, which leads to the formation of cytotoxic oxygen intermediates. Fifty-four Sprague-Dawley rats underwent injection of 0.3 ml doxorubicin solution (2 mg per milliliter) intradermally on both flanks as described by Rudolph and colleagues. Group I (N = 28) received HBO treatment (2 hours at 2 ATA) for 3 days prior to injection and 7 days postinjection. Group II (N = 26) received no HBO treatment. At 2, 3, and 5 weeks, the size of the ulcers

and the surrounding area of alopecia in group I (+HBO) were significantly larger than in group II (-HBO): 112.2 mm2 vs. 42.8 mm2 (p < 0.01) and 1,132.2 mm2 vs. 364.8 mm2 (p < 0.005). Biochemical analysis of the biopsied skin ulcers, to measure the parameters of oxygen free radical production, indicated (similar) low levels of xanthine oxidase for both groups. However, significantly elevated levels of malonyldialdehyde (MDA), indirect evidence of free radical production, was observed in group I (+HBO) in comparison with group II (-HBO): 36.58 vs. 5.84 ng per minute per milligram protein (p < 0.001), which might indicate free radical-induced cellular injury. It is concluded that in this animal study the cytotoxicity of doxorubicin is potentiated by HBO therapy. The elevated levels of MDA suggest a direct additive cytotoxic effect by increased membrane lipid peroxidation. HBO therapy, therefore, might be deleterious in the early (preulcer) stage of doxorubicin extravasation.

[17] Twillman RK, Long TD, Cathers TA, Mueller DW. Treatment of painful skin ulcers with topical opioids. *J Pain Symptom Manage*. 1999;17(4):288-292. PMID: 10203881.

Recent research suggests that opioid receptors on peripheral nerve terminals may play an important role in the modulation of pain. Clinical applications of this knowledge have been rather slow to evolve. We describe a consecutive series of nine patients with painful skin ulcers due to a variety of medical conditions. All patients were treated with a topical morphine-infused gel dressing. Seven of the nine patients experienced substantial and another experienced a lesser (but still significant) degree of analgesia. The ninth reported no relief, but his wound was not an open ulcer. Discussion centers on the practical application of this development in the large number of patients with painful skin lesions.

[18] Zeppetella G, Paul J, Ribeiro MD. Analgesic efficacy of morphine applied topically to painful ulcers. *J Pain Symptom Manage*. 2003;25(6):555-558. PMID: 12782436.

The analgesic effects of morphine applied topically to painful ulcers was assessed in a randomized, double-blind, placebo-controlled, crossover pilot study of five patients with painful sacral sores. Patients were treated for two days with either 10 mg morphine sulfate or placebo (water for injection) applied topically to the ulcer. After a two-day wash-out period, patients were crossed over for a further two days of the alternative treatment. Patients were asked to rate analgesia using a visual analogue scale (VAS) and to document any local or systemic adverse effects. All patients reported lower VAS scores with morphine compared to placebo and no local or systemic adverse events attributable to morphine were noted by either patients or nursing staff. This pilot study suggests that morphine applied topically is an effective method of producing local analgesia, well tolerated by patients, and not associated with systemic adverse effects.