Review on Alloxan induced diabetic foot ulcer (wound healing)

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Abstract: Diabetes mellitus: Complications of diabetes mellitus include problems that develop rapidly (acute) or over time (chronic) and may affect many organ systems. Most of the organs gets damaged during the diabetes. Diabetic foot ulcer is one of the disorder. Diabetes mellitus is a metabolic disease with deficiency of secretion or action of endogenous insulin, features of hyperglycemia.

Keywords: Diabetes mellitus, diabetic foot ulcer, wound healing, Alloxan

Introduction: History of Diabetic foot ulcer: The alloxan model of diabetes was first described in rabbits by Dunn, Sheehan and McLetchie et al in 1943. The name is derived from allantoin, a product of uric acid excreted by the fetus into the allantois, and oxaluric acid derived from oxalic acid and urea, found in urine. (4) Alloxan causes diabetes by a mechanism which basically involves partial degradation of the beta (β) cells of pancreatic islets and subsequent compromise in the quality and quantity of insulin produced by these cells.

Diabetic foot ulcer: Diabetic foot ulcer is a major complication of diabetes mellitus, and probably the major component of the diabetic foot. Wound healing is an innate mechanism of action that works reliably most of the time. A key feature of wound healing is stepwise repair of lost extracellular matrix (ECM) that forms the largest component of the dermal skin layer. 2,3 Ulcers form due to a combination of factors, such as lack of feeling in the foot, poor circulation, foot deformities, irritation (such as friction or pressure), and trauma, as well as duration of diabetes. Patients who have diabetes for many years can develop neuropathy, a reduced or complete lack of ability to feel pain in the feet due to nerve damage caused by elevated blood glucose levels over time. The nerve damage often can occur without pain and one may not even be aware of the problem. Your podiatric physician can test feet for neuropathy with a simple and painless tool called a monofilament.

Symptoms of diabetic foot ulcer:
- Any changes to the skin or toenails, including cuts, blisters, calluses or sores.
- Discharge of fluid or pus.
Foul smell.
- Pain.
- Redness.
- Skin discoloration.
- Swelling.
- Darkened skin on the affected area.
- Diminished ability to sense hot or cold.
- Loss of hair in the area.
- Numbness.
- Tingling.
- Any changes to the skin or toenails, including cuts, blisters, calluses or sores.

Diabetic foot ulcer mainly occurs in people who have:
- Nerve damage or poor blood flow in the feet.
- Trouble managing blood glucose levels over long periods, including frequent episodes of hyperglycemia (blood sugar that’s too high).
- Weight problems.
- Had diabetes for a long time.
- High blood pressure or high cholesterol.

The chance that a person with diabetes will develop a foot condition at some time in their life is about 15%.

Causes diabetes-related foot conditions:

1. Long-term high blood sugar can cause a type of nerve damage called diabetes-related neuropathy. Diabetes-related neuropathy can occur throughout the body, but most often in the legs and feet.
2. The condition might make you lose feeling in your feet. If your feet are numb, you might not notice a blister, cut or sore. You might not even feel a pebble in your sock that is cutting your foot, for example. Wounds that go unnoticed and untreated can become infected.
3. Diabetes can also affect blood flow to your legs and feet. People with diabetes are more likely to develop peripheral artery disease (PAD). This condition causes arteries to become narrowed or blocked. Reduced blood flow (poor circulation) can make it difficult for a diabetes-related foot ulcer or infection to heal.

Treatment:


2. Antibiotics:

Recent infection of superficial wound (< 1Month) Cloxacillin or cephalaxin or [amoxicillin + clavulanate] or clindamycin
3. Growth factor: E.g. Becaplermin gel or Regranex (Human recombinant platelet derived growth factor)

4. Other treatment option:
   a) Wound dressing E.g. Hydrogel dressing
   b) Negative pressure wound therapy
   c) Hyperbaric oxygen therapy

Other Treatment may include:

- Cleaning the wound.
- Draining any fluid or pus from the ulcer.
- Removing or cutting away dead or infected tissue (called debridement).
- Applying special bandages and ointments to absorb extra fluid, protect the wound and help it heal.
- Prescribing a wheelchair or crutches to take weight off the affected foot (called offloading).
- Prescribing oral or IV antibiotics to control and eliminate infection.
Things to Avoid:

- Cut calluses or corns or apply chemicals.
- Smoke.
- Soak your feet.
- Walk around barefoot.
- Wear tight socks or shoes.

Alloxane induced Diabetes:

Alloxan is toxic glucose analogues that preferentially accumulate in pancreatic beta cells via the GLUT2 glucose transporter. In the presence of intracellular thiols, especially glutathione, Alloxone generates reactive oxygen species (ROS) in a cyclic redox reaction with its reduction product, dialuric acid. Autoxidation of dialuric acid generates superoxide radicals, hydrogen peroxide and, in a final iron-catalysed reaction step, hydroxyl radicals. These hydroxyl radicals are ultimately responsible for the death of the beta cells, which have a particularly low antioxidative defense capacity, and the ensuing state of insulin-dependent ‘alloxan diabetes. Alloxan has two distinct pathological effects: it selectively inhibits glucose-induced insulin secretion through specific inhibition of glucokinase, the glucose sensor of the beta cell, and it causes a state of insulin-dependent diabetes through its ability to induce ROS formation. Alloxane is most popular diabetogenic agents used for assessing the ant diabetic or hypoglycemic capacity of test compounds. Notably, Alloxan is far less expensive and more readily available.

Drugs used for treatment of diabetic foot ulcer:

Agents such as cephalaxin, dicloxacinil, amoxicillin-clavulanate, or clindamycin are effective choices. If methicillin-resistant *S. aureus* (MRSA) infection is suspected, then clindamycin, trimethoprim-sulfamethoxazole, minocycline, or linezolid may be used.

Becaplermin (Regranex)

Becaplermin gel 0.01% (Regranex), a recombinant human PDGF that is produced through genetic engineering, is approved by the US Food and Drug Administration (FDA) to promote healing of diabetic foot ulcers.

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<table>
<thead>
<tr>
<th>Severity of infection</th>
<th>Additional factors</th>
<th>Usual pathogen(s)</th>
<th>Potential empirical regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (usually treated with oral agents)</td>
<td>No complicating features</td>
<td>MSSA, <em>Streptococcus</em> spp.</td>
<td>1st generation cephalosporin, nafcillin, ampicillin/sulbactam, amoxicillin/clavulanate, clindamycin</td>
</tr>
<tr>
<td>β-lactam allergy or intolerance</td>
<td>MSSA, <em>Streptococcus</em> spp.</td>
<td>Clindamycin, levofloxacin, moxifloxacin, doxycycline</td>
<td></td>
</tr>
<tr>
<td>Recent antibiotic exposure</td>
<td>MSSA, <em>Streptococcus</em> spp., Gram-negative rods</td>
<td>Levofloxacin, moxifloxacin, 2nd or 3rd generation cephalosporin</td>
<td></td>
</tr>
<tr>
<td>High risk for MRSA</td>
<td>MRSA</td>
<td>Clindamycin, trimethoprim/sulfamethoxazole, doxycycline</td>
<td></td>
</tr>
<tr>
<td>Moderate (oral or initial parenteral) or Severe (parenteral)</td>
<td>No complicating features</td>
<td>MSSA, <em>Streptococcus</em> spp., ± Gram-negative rods</td>
<td>2nd or 3rd generation cephalosporin±aminoglycoside</td>
</tr>
<tr>
<td>Recent antibiotic exposure</td>
<td>MSSA, <em>Streptococcus</em> spp., ± Gram-negative rods</td>
<td>3rd generation cephalosporin±aminoglycoside, ertapenem, piperacillin/tazobactam, cefepime</td>
<td></td>
</tr>
<tr>
<td>Macerated ulcer and warm climate, Ischemic limb/necrosis/gas forming</td>
<td>Gram-negative rods, including <em>Pseudomonas</em></td>
<td>Piperacillin/tazobactam, cefepime, imipenem, meropenem</td>
<td></td>
</tr>
<tr>
<td>MRSA risk factors</td>
<td>MRSA ± <em>Streptococcus</em> spp., ± Gram-negative rods</td>
<td>Vancomycin or teicoplanin + 3rd generation cephalosporin, cefepime, piperacillin/tazobactam, ertapenem</td>
<td></td>
</tr>
<tr>
<td>Risk factors for resistant Gram-negatives</td>
<td>ESBL, multi-drug resistant Gram-negatives</td>
<td>Piperacillin/tazobactam±aminoglycoside, imipenem, meropenem</td>
<td></td>
</tr>
</tbody>
</table>

### Antibiotics treatment:

Antibiotics expecting that they will prevent infection and promote wound healing, even if diabetic foot ulcers are not infected; however, there is no evidence to support this assumption. Overuse of antibiotics increases the incidence of adverse events, antibiotic resistance, and cost. Therefore, it is recommended that antibiotics not be prescribed for clinically uninfected wounds to prevent infection or promote wound healing. When classic signs of infection (erythema, edema, heat, pain, and purulent discharge) are not clear due to ischemia and neuropathy in diabetic foot wounds, secondary signs of infection such as serous exudate, delayed healing, friable granulation tissue, discolored granulation tissue, foul odor, pocketing of the wound base, and wound breakdown can be taken
as an evidence of infection. In these unusual cases, it may be appropriate to administer a brief course, culture-directed antibiotic and observe the therapeutic response.

Empirical antibiotics are initially selected based on the clinical features, disease severity, and local antimicrobial resistance patterns in the patients with DFIs. Narrow-spectrum oral antibiotics can be administered for mild infections and broad-spectrum parenteral antibiotics administered for to severe infections. Oral or parenteral antibiotics can be administered for moderate infections according to the patient’s circumstances. An empiric regimen should always include antibiotics active against standard strains of *Staphylococcus* and *Streptococcus* species and, in some specific situations, include antibiotics active against Gram-negative rods, MRSA, *Pseudomonas*, MDR pathogens, and anaerobes. It is not clear if any one systemic antibiotics treatment is better than others in resolving infection or in terms of safety, except that tigecycline is significantly less effective and associated with more adverse effects than ertapenem (± vancomycin). Empirical antibiotics are listed above.

References:


