**Smallpox Update**

What is smallpox?

Smallpox is caused by the variola virus, a DNA virus that emerged thousands of years ago. It belongs to the orthopoxvirus family, which also includes monkeypox, camelpox and cowpox. The last case of smallpox reported in the U.S. was in 1949 and eradication was declared in 1980. The smallpox vaccination program was discontinued in 1972, meaning that most people under the age of 30 in the U.S. are not vaccinated. The incidence of smallpox is highest in the winter and early spring because the virus thrives in low humidity and cooler temperatures. Smallpox is spread mainly by inhalation of the virus in respiratory droplets; it is not transmitted by insects or animals. Direct contact with body fluids or contaminated objects is also a mode of transmission.

The World Health Organization (WHO) developed a classification system for the smallpox virus. The 2 main types are variola major and variola minor. Within the variola major category, 4 strains exist. The ordinary strain accounts for 90% of smallpox cases and has a 30% fatality rate. The modified strain is rarely fatal and affects mainly previously vaccinated patients. The flat and hemorrhagic strains are both rare but carry a 97 to 100% fatality rate. Less than 1% of those who have variola minor will die from smallpox. Death from smallpox is usually a result of toxemia and hypotension.

How is smallpox spread?

Upon exposure to smallpox, the virus enters the respiratory tract and implants itself into the respiratory mucosa. During this incubation period, the virus migrates to the lymph nodes and begins to multiply. At this time the patient is not contagious and may be unaware that he is infected. The incubation period can last from 7 to 17 days. Next, the prodromal phase begins where the patient may experience severe headaches, backaches, malaise or fevers. This lasts 2 to 3 days and is usually not contagious. The early rash begins over 1 to 2 days and is usually first seen on the face and extremities. It will appear as small reddish macules 2-3 mm in diameter and eventually spread to cover the entire body. All the lesions will evolve at the same rate. This is the most contagious period of smallpox. The macules develop into round firm pustules and eventually become 2-5 mm vesicles filled with fluid. After about 5 days, the vesicles begin to crust and scab over. The scabs will finally resolve and fall off leaving pitted scars. The patient is not considered as contagious after the scabs have disappeared. Sixty to 80% of survivors will be left with pockmarks. About 1% will develop blindness due to viral keratitis and less than 1% will have encephalitis. Table 1 illustrates the progression of smallpox and which phases are considered contagious.

<table>
<thead>
<tr>
<th>Duration</th>
<th>Contagious</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation</td>
<td>7-17 days</td>
<td>No</td>
</tr>
<tr>
<td>Prodrome</td>
<td>2-4 days</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Early rash</td>
<td>4 days</td>
<td>Most</td>
</tr>
<tr>
<td>Pustules</td>
<td>5 days</td>
<td>Yes</td>
</tr>
<tr>
<td>Scabs</td>
<td>5 days</td>
<td>Yes</td>
</tr>
<tr>
<td>Resolving scabs</td>
<td>6 days</td>
<td>Yes</td>
</tr>
<tr>
<td>Resolution</td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>
How do you diagnose and treat smallpox?

Smallpox is diagnosed mainly by the characteristic rash. In addition, electron microscopic examination of the pustule fluid, polymerase chain reaction (PCR) and growth of the virus in cell culture are used to confirm the diagnosis of smallpox. There are currently no approved treatment options for this virus. Immediate action should be taken once a smallpox patient has been diagnosed. The patient should be placed in a negative pressure room and kept in respiratory and contact isolation. If the patient is still in the early phase of the infection, vaccination of the patient may be beneficial. Supportive care, especially hydration and nutrition, are the mainstays of treatment. Antibiotics should be used if the patient has widespread eruptions of the lesions or if they develop secondary infections. Ophthalmic antibiotics are used in the event of eye infections.

What vaccines are available?

There are currently 2 vaccines available and 1 vaccine in development and production. Dryvax (Wyeth) is the only vaccine commercially approved for use in the United States. Aventis-Pasteur also makes a similar vaccine but it is only available as a reserve supply. These 2 vaccines were developed 20 to 30 years ago from the lymph of calves. There are 375 million diluted doses available, which is enough for the entire U.S. population in the event of a smallpox outbreak. Acambis – Baxter is currently developing a new vaccine using the same strain of smallpox as the Dryvax vaccine. This vaccine is derived from monkey kidney and human fibroblast cells and will replace the Wyeth and Aventis-Pasteur vaccines when 209 million doses become available in 2004.

Live vaccinia virus contained in the smallpox vaccine is closely related to the variola virus which causes smallpox. Ninety-five percent of people receiving the vaccinia virus vaccine will exhibit immunity to smallpox. After inoculation, complete immunity (protection from contracting the smallpox virus) is expected to last 3-5 years, while partial immunity may persist for 10 years or longer. Persons with partial immunity may contract smallpox, but have a milder form of the disease and a decreased risk of mortality or severe side effects. A bifurcated needle is dipped into the vaccine and applied to the dermis of the upper deltoid muscle using 15 pokes. Within 3 to 4 days, a red itchy bump develops and progresses into a large blister filled with pus. During the second week, the blister dries up and scabs over. The scab will fall off during the third week.

What are the risks associated with the vaccine?

Since the last immunizations in the US were given in 1972, the majority of exposed individuals will require revaccination in the event of a smallpox outbreak. Smallpox vaccine administered within 3-4 days of exposure may protect from infection or at least diminish disease severity. Even 4-7 days post-exposure, vaccination may still offer modest benefits. It is recommended that those people who may come in direct contact with the smallpox virus be vaccinated. They include healthcare workers, military personnel, and anyone who may be exposed. There are a number of people who should not receive the smallpox vaccine.

Pre-event Vaccine contraindications:

Pre-event vaccination is not recommended for certain groups considered to be at increased risk of vaccination related complications. Smallpox vaccination contraindications are described as follows:

Cardiovascular Contraindications

Ten cases of cardiovascular adverse events have been observed in the 29,584 civilians vaccinated in the period from January 24 to March 28, 2003. Civilian events include 4 cases of myocarditis and/or myopericarditis and 2 cases of angina, none of which were fatal. Additionally, 4 myocardial infarctions have been noted, 2 of which were fatal. The Department of Defense has reported 14 cases of myocarditis from the group of approximately 250,000 service personnel receiving the smallpox vaccination for the first time. An estimated 365,000 military members have been vaccinated to date, and 1 fatal myocardial infarction has occurred. Rare cases of myocarditis and pericarditis had previously been reported in Europe and Australia where a more virulent form of vaccinia had been used for the smallpox vaccine. However, myocarditis and pericarditis had not been commonly reported in the US where a less virulent form of vaccinia was used in vaccinations. The cardiac adverse events have been temporally associated with the smallpox vaccine but causality has not been established at this time. Experts are working to determine if the adverse events were related to the smallpox vaccine or purely coincidental, since the number of ischemic cardiovascular events is consistent with rates of heart disease expected in the general public. However, as a precautionary measure, persons with known heart disease or risk factors should not receive the vaccine at this time.

Cardiovascular contraindications include:
- Any diagnosis of heart disease.
- Previous angina or myocardial infarction.
- Previous or current diagnosis of heart failure or exertion.
- Transient ischemic attack or stroke.

Patients having 3 or more of the following risk factors should also be excluded from vaccination:
- Hypertension.
- Hypercholesterolemia.
- Diabetes, or pre-diabetes.
- Current smoking.
- First degree relative diagnosed with heart disease before the age of 50.

Five of the 6 civilian patients experiencing ischemic cardiac adverse events (myocardial infarction or angina) fulfilled the above exclusion criteria. Any vaccinated person experiencing chest pain or shortness of breath should seek medical attention immediately.
Postvaccinal encephalitis is another complication that has occurred in 1 person for every 300,000 vaccinated. Twenty five percent of those people who develop encephalitis will die. Overall, the death rate from receiving the vaccine was 3 people per 1 million vaccinated. Vaccinia can be treated using vaccinia immune globulin (VIG). This contains anti-vaccinia neutralizing antibody and is given as an IM injection. Cidofovir (Vistide) is currently used for the treatment of CMV retinitis but has shown in vitro activity against the poxviruses. This is available only as an investigational agent in the treatment of vaccinia.

Persons with the following conditions should not be vaccinated. Persons considering vaccination who reside in the same house or have close physical contact with individuals experiencing these conditions should also not be vaccinated at this time.

- Atopic dermatitis, eczema, Darier’s disease, or other exfoliative skin conditions.
- Diseases that compromise the immune system: human immunodeficiency virus (HIV), acquired immune deficiency syndrome (AIDS), systemic lupus, or other severe autoimmune diseases.
- Medications or treatments causing immunosuppression including: radiation, chemotherapy, high-dose corticosteroids (for example ≥ 20 mg of prednisone per day), or immunosuppressive agents used for organ or stem cell transplant.
- Smallpox vaccination is contraindicated in pregnancy. Pregnancy should also be avoided for 4 weeks following vaccination.

Contraindications, which apply only to the person receiving the vaccination, include:

- Allergic reaction to smallpox vaccine or allergy to the following agents, which may be found in the vaccine or diluent: neomycin sulfate, streptomycin sulfate, chlorotetracycline hydrochloride, polymixin B sulfate, phenol or glycerin.
- Children < 1 year of age. (Pre-event vaccination is not recommended in persons < 18 years of age.)

Persons with these conditions should postpone vaccination until the disease resolves:

- Exfoliative acute or chronic skin conditions including: chicken pox, impetigo, shingles, herpes, severe acne, or psoriasis.
- Eye infections or use of steroid drops in the eyes.
- Acute illness of moderate to severe intensity.

Pre-event smallpox vaccination is not recommend for women who are breastfeeding.

**Vaccine contraindications:**

There are no absolute contraindications to vaccination in the event of a smallpox exposure, and the CDC recommends vaccination of anyone directly exposed to smallpox virus. Public health officials would additionally advise individuals regarding vaccination based on the level of threat and disease risk. Additional information about the smallpox vaccine, contraindications, and adverse events is available on the CDC website at: [http://www.bt.cdc.gov/agent/smallpox/index.asp](http://www.bt.cdc.gov/agent/smallpox/index.asp).

**What is currently being done?**

Two stores of live variola virus are kept at the Center for Disease Control and Prevention (CDC) in Atlanta, Georgia, and at The Institute of Virus Preparations in Moscow, Russia. However, intelligence information suggests that several other countries may possess unapproved variola stocks. The terrorist attacks of September 11, 2001 and anthrax release in October 2001 highlight the real potential of biological warfare. Smallpox is one of the most devastating of all infectious diseases and has been viewed as an ideal candidate for biological weapons.

The federal government has developed a vaccination plan consisting of 3 phases. Phase I will entail vaccination of public health department teams who would be the first to respond to a smallpox outbreak. Phase II is vaccination of emergency workers such as paramedics and police officers. The general public will be vaccinated on a voluntary basis during Phase III of the federal plan. Smallpox healthcare teams have also been developed at state and city levels. The purpose is to create a team of vaccinated healthcare workers who will be trained to provide medical care in the event of an outbreak. They will evaluate and manage patients in the emergency department and provide hospital based care for the first 7 to 10 days after diagnosis. It is recommended that the teams consist of physicians and nurses from the emergency department, intensive care units, general medical units and medical subspecialties. In addition the teams would also contain infection control personnel, respiratory therapists, radiology technicians, security, and housekeeping staff. These teams would be available on a 24 hour basis.

To prepare for terrorist attack, the US government has stockpiled enough vaccine to adequately vaccinate the entire population. Emergency preparedness plans have been established to vaccinate the public in the event of a smallpox virus release. Currently, emergency response personnel and health care workers who will be providing vaccinations and treating smallpox cases are voluntarily receiving the vaccine.

**Pros and Cons of Sliding Scale Insulin**

Recent statistics suggest that there are approximately 3.6 million people in the United States on some form of insulin therapy. Insulin is administered as an adjunct to oral therapy, or on a as-needed basis. Recommendations set forth by the American Diabetes Association, suggest a preprandial plasma glucose level of 90 to 130 mg/dl, a postprandial plasma glucose of less than 180mg/dl, and a hemoglobin A1c of less than 7.0%. For many patients, achievement of these recommendations is very difficult. It requires extensive self-monitoring, frequent physician visits, and close observance to lifestyle modifications. In an attempt to achieve optimal glucose control, minimize the risks of hypo/hyperglycemia, and
reduce long-term complications, physicians frequently change their patient’s drug and insulin regimens. Historically, outpatient insulin therapy was administered based on urine glucose levels. The dose of insulin, depended on urine glucose measurements. Hyperglycemic episodes frequently occurred as a result of the lag time between hyperglycemia and glucosuria. Once blood glucose monitors became available, insulin regimens were individualized based on the patient’s blood level or immediate needs. This led to the advent of "insulin adjustment protocols", very similar to the sliding scale regimens of today. Supplemental insulin doses were given based on the glucose meter reading and proximity to mealtime.

Physicians, who were schooled with sliding scale insulin regimens, appreciated the simplicity of the approach. Initially, sliding scale insulin regimens were thought to save time for physicians’, pharmacists’, and nurses’. In reality however, sliding scale regimens required management by the nursing staff who often times had to notify physicians of extremes in plasma glucose levels.

The American Diabetes Association annually publishes a position statement on the care of diabetic patients. Sliding scale insulin is not mentioned in the 2003 guidelines; however, they do state that aggressive glycemic control is fundamental to diabetes management. The management plan is described as an individualized therapeutic alliance between all healthcare providers, family, and the patient. Furthermore, aggressive glycemic control should be adequate enough to prevent hyperglycemic crisis, therefore negating the “need” for sliding scale insulin use.

There appears to be limited support for sliding scale regimens in the medical literature. Dickerson et al investigated glycemic control in medical inpatients with type 2 DM receiving sliding scale insulin regimens compared with "routine" therapy. It was determined that there is no statistical difference in hyperglycemia, length of hospitalization in either group of patients. However, most studies that investigated inpatient insulin regimens, found that standing insulin regimens provided superior blood glucose management when compared to sliding scale insulin therapy. Queale et al investigated sliding scale insulin as a means for glycemic control in a prospective cohort study of 171 adults admitted to hospitals with diabetes mellitus. Results demonstrated that sliding scale insulin therapy was associated with a 3 fold higher risk of hyperglycemia when used as the sole glycemic control regimen. Furthermore, there was no benefit in patients when sliding scale insulin was used as an addition to a standing regimen of long-acting insulin, length of hospitalization in either group of patients. There are multiple regimen choices for sliding scale insulin dosing, all based on the same principles. The units of insulin administered are dependent on the most recent glucose meter reading. However, this method forgets to include adjustments for meal times, size of meals, diurnal variations in individual patients, and most importantly, differences in glucose and insulin utilization in individual patients. A sample sliding scale regimen is as follows:

<table>
<thead>
<tr>
<th>Blood Glucose Concentration</th>
<th>Units of Insulin Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>151-200mg/dl</td>
<td>2 units</td>
</tr>
<tr>
<td>201-250mg/dl</td>
<td>4 units</td>
</tr>
<tr>
<td>251-300mg/dl</td>
<td>6 units</td>
</tr>
<tr>
<td>301-350mg/dl</td>
<td>8 units</td>
</tr>
<tr>
<td>351-400mg/dl</td>
<td>10 units</td>
</tr>
<tr>
<td>401-450mg/dl</td>
<td>12 units</td>
</tr>
<tr>
<td>&gt; 450mg/dl</td>
<td>page MD</td>
</tr>
</tbody>
</table>

The main issue with sliding scale is that it treats a particular blood glucose reading without regarding other factors - meal time/size, differences in glucose and insulin utilization, diurnal variations. Sliding scale insulin is at best, a post-hyperglycemic fix that does not address the underlying condition. Basal insulin requirements are not met with sliding scale insulin, hence the hyperglycemic state it serves to treat. Large swings in blood glucose are promoted, not corrected, by the use of sliding scale insulin as the sole regimen for glycemic control.

This is not to say that supplemental insulin is entirely without merit. There is a role for supplemental insulin in carbohydrate counting, especially for insulin pump patients. The use of supplemental insulin algorithms, which address insulin dosing and administration time, diet, physical activity, and other factors that can alter glucose levels, are very beneficial when used appropriately. They help to address the timing of insulin administration, type of insulin (long vs. intermediate vs. short acting), and the basal insulin requirement of the individual patient according to caloric intake and expenditures. Supplemental doses are generally administered prior to a meal or snack to prevent or correct an undesired blood glucose level. These doses are normally given with a 15-20 minute lag time before food ingestion. Inpatient administration of supplemental insulin has an added benefit to glucose control- it also allows health care workers to educate the patient on proper use and administration of insulin at home by allowing the patient to inject while in the hospital under their supervision. Sliding scale insulin, or supplemental insulin, use in the management of inpatient post-operative patients, severely ill patients with history of severe diabetic complications, steroid use, and high admission plasma glucose level may be beneficial and necessary in addition to their standing regimen. The patient’s standing regimen may be adjusted according to patient response and clinical evaluation. These patient types may be under high stress, and requirements may change acutely, therefore a supplemental insulin regimen may decrease the stress burden, helping to improve healing.

The following excerpt is a comment by William S. Queale, MD, MS, and Frederick L. Brancati, MD, MHS published in the Osler Medical Journal regarding the fallacy of thought behind the use of sliding scale insulin regimens. It may seem like a ridiculous analogy, but is it really that different?
A 62-year-old woman with a history of hypertension is admitted to the hospital with cellulitis. She takes nifedipine XL 90 mg per day and has a blood pressure of 162/88 on admission. You treat her hypertension by discontinuing her nifedipine and writing the following orders: check blood pressure every six hours; for a systolic blood pressure (SBP) between 100-150 give no nifedipine; for a SBP between 151-200 give 10 mg nifedipine; for a SBP between 201-250 give 20 mg nifedipine; for a SBP between 251-300 give 30 mg nifedipine; for a SBP > 300 notify house officer.

Sliding scale insulin use is widespread here at UIC. Most diabetic patients are continued on their current regimens, and then physicians order sliding scale insulin to cover immediate episodes of hyperglycemia evidenced by glucose meter readings. Further research is needed to address glycemic control in inpatient use, and until then, no definitive recommendations can be made with regards to sliding scale insulin.

**Adult Critical Care Drip Sheet**

The Adult Critical Care Drip Sheet list is now available. The list includes infusion information for 35 medications. Information includes standard concentration, standard dilution, standard fluid and alternative fluid, common adult administration rate, and, if known, maximum administration rate and maximum concentration. Additionally, information is included for IV compatibility among 23 medications.

The purpose of this document is to provide information to clinicians that will improve the safety of using these high-risk medications. For example, limiting or standardizing concentrations available for use in the hospital helps to minimize the opportunity for dose and infusion rate calculation errors. Also, maximum administration rate provides a guideline for nurses that may need to titrate a medication to the patient’s response. Readers who wish to review this list may do so by opening the attached word document.

In the near future, Gemini will be updated to provide these concentrations and common adult administration rates to facilitate the ordering process.

**Heparin Dosing Rule**

Heparin dosing clinical decision support rule was implemented in May. This Rule triggers on heparin IVP and IV orders and searches for a recent (within 48 hours) PTT result and patient’s weight. An alert is triggered if there is no weight, recent PTT results or if the heparin dose is not consistent with the P&T approved heparin dosing guidelines. Based on patient specific information, heparin dosing recommendation alert is displayed. The user has the option to enable the allergy, height and weight form from within the alert and enter patient’s weight. The Heparin Dosing Rule also triggers when a PTT result is posted to the flowsheet. If the PTT result is not within therapeutic range and there is an active order for IV heparin, a dosing adjustment text prints at the patient’s nursing unit.

**P&T Update - March 2003**

**Additions**
- Rituximab
- Histidine-tryptophan-ketoglutarate organ preservation solution (Custodial HTK™)
- Line Extensions
- Budesonide AQ nasal spray

**Not Added**
- Tegaserod

**Deletions**
- Viaspan organ preservation solution
- Fondaparinux
- Due to low use or manufacturer discontinuation
- Idarubicin injection
- Primadone suspension
- Procaine injection
- Trifluoperazine 10mg tablet
- Acetic acid/aluminum acetate otic
- Zinc oxide paste
- Budesonide nasal spray
- Neomycin ointment

**P&T Update - May 2003**

**Additions**
- Glargine insulin 100 units/ml injection
- Aripiprazole 10mg, 15mg tablet
- Ezetimibe 10mg tablet

**Deletions**
- Ultralente insulin
- Lente insulin
- Atorvastatin
- Trifluoperazine
- Due to low use or manufacturer discontinuation
- Hyaluronidase
- Sodium tetradecyl sulfate
- Anthralin cream
- Auranofin
- Aurothioglucose
- Methylsalicylate ointment
- Trifluridine ophthalmic solution
- Triple sulfa vaginal cream
- Tretinoin gel, cream, solution
- Aminess 5.2% injection
- Mumps skin test antigen

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