Tuberculosis (TB) is the second leading cause of death WORLDWIDE from a single infectious pathogen. Despite the fact that the majority of TB cases are in developing countries, this disease is also a problem in industrialized nations, such as the United States. *Mycobacterium tuberculosis* infects approximately 15 million people in this country, although it causes disease in many fewer. Even though this number is low compared to other countries, effective screening and treatment of latent infection is necessary to prevent new cases from emerging. After a healthy person is infected with *M. tuberculosis*, they have about a 10% lifetime risk for developing active TB. The highest risk for healthy patients occurs in the first 2 years after infection. The risk for conversion to active TB is increased among groups, such as children under the age of 2 and patients with comorbid conditions resulting in immunosuppression. The highest risk is associated with patients that have human immunodeficiency virus (HIV) infection. This risk is about 100 times higher than the normal population. In addition to the increased risk of active TB in HIV, TB may also have a detrimental effect on HIV. Due to the severity of active TB and the availability of medications to prevent it, effective testing for TB infection is necessary in high risk patients.

The purified protein derivative (PPD) tuberculin skin test is the most widely used diagnostic tool for identifying TB infection. It is the best available test for screening at the moment. However, the test is less than 100% sensitive and specific. The test is based on the concept of delayed type hypersensitivity (DTH) reactions. If the patient is infected with *M. tuberculosis*, then they should have T cells sensitized to the mycobacterium. Those sensitized T cells would be recruited to the site where the PPD was injected intradermally and would evoke a reaction measured by induration of the site. The recommended technique is the Mantoux method. This is where 0.1 ml of the 5-TU PPD is injected intradermally on the volar surface of the forearm. The induration of the area is read 48-72 hours after the injection.

The results are valuable only if one understands the limitations of the test in terms of the validity of positive and negative results. The validity of a positive result is dependent on the prevalence of TB infection in that particular patient group. If the rate of infection or exposure to *M. tuberculosis* is low in that particular group, then the positive result is more likely to be a false-positive. It is no longer recommended to screen patients with a low risk of infection or exposure to TB. However, in patients that are at high risk for infection, due to close contact to active TB patients or the areas they live in, the PPD test is more specific and a positive test is likely to be indicative of a true infection. The Centers for Disease Control and Prevention (CDC) now recommends targeted testing, where patients that are at high risk for infection or for progression to active disease (i.e. HIV) are the primary patients screened for TB infection. Guidelines also state that different measurements of induration indicate positive results for different patient groups (table 1).

As mentioned above, some positive PPD results may actually be false-positives. This error is sometimes caused by infection with other mycobacteria and previous vaccination with bacillus Calmette-Guerin (BCG) vaccine. Some of the antigens that are in the PPD test are similar to other mycobacteria and can lead to a false-positive skin reaction. Patients with previous BCG vaccination can also have a skin reaction which could possibly be a false-positive. However, these patients come from areas in the world where TB is prevalent and any sign of a positive test based on findings as seen in table 1 should be examined and
treated appropriately, due to their high risk of being infected. In addition, there is also a risk for patients to have false-negative tests. There are a multitude of reasons why patients may have false-negative results. Different patient characteristics can alter the result of the test and they are detailed in table 2. False-negative results can also occur due to factors controlled by the health care practitioner (HCP). For example, the tuberculin that is administered could be improperly stored, diluted, or contaminated. The HCP could also improperly administer the PPD by injecting it subcutaneously, or to close to other skin tests. Also, the test may be a false-negative if not enough antigen is injected or if there is a delay in administering after the PPD is drawn up in the syringe. Finally, if the HCP is not properly trained at reading the PPD skin test, there can be errors in recording the result.

As seen in table 1, the lowest cutoff point of 5 mm is for patients that have a high risk for progression into active TB disease. This lower cutoff is designed to make sure that infected patients are detected. However, another problem with these patients exists, primarily the HIV-positive patients. Due to their immunocompromised state, HIV-positive patients are not always able to mount a DTH reaction to the PPD test. Their inability to react to the PPD test, when in fact they are infected, is due to what is called cutaneous anergy. Anergy is the inability to mount a DTH reaction to an antigen that the body has been exposed to before. There are 2 types of anergy: specific and generalized. Specific anergy is where the patient does not produce a response to an antigen to which they have been exposed, but still responds to other antigens. Generalized anergy is where the patient can not produce a reaction to any antigen. Many HIV-positive patients are good examples of generalized anergy. Due to their immunosuppression, they have impairment in the cellular components needed to mount the DTH reaction. Since, some HIV patients may have anergy, it is difficult to assess whether a negative response is truly negative. So, in the 1970’s, anergy testing became common practice to help determine whether negative PPD results for immunosuppressed patients were true negatives.

Anergy testing is based on the concept that if the patient was exposed to other antigens, such as mumps, and they had a DTH reaction, then the practitioner could assume that his or her negative PPD test was truly negative. In 1991, the CDC recommended that anergy panels be used in adjunct with PPD tests in HIV positive patients because it was shown that PPD positivity was inversely related with anergy and CD4 cell counts. Anergy panels usually consist of injecting 2 different antigens intradermally using the same method as PPD tests. The problem is that there is no standard protocol for determining what a positive response is, how many antigens should be tested, or which antigens are appropriate. Also, due to the fact that some patients have specific anergy it is hard to extrapolate what the results actually mean. This means that some people may be responsive to different antigens such as mumps but no longer respond to PPD tests, even if they are infected with TB. It has also been seen that some patients still can respond to PPD tests even if they do not respond to other antigens in the anergy panels. With this lack of correlation between testing for anergy and whether a PPD test is truly negative, the CDC no longer recommends using anergy tests in addition to PPD tests in HIV positive patients.

In summary, the CDC and most experts no longer recommend anergy testing be used as a routine adjunct to PPD tests, even in the HIV infected population. Despite the old recommendations and the sound theory behind its use, it leads to misleading conclusions. The only valuable and useful test is a positive PPD test. Negative results are confusing in the HIV-positive population, especially due to their high risk of TB disease. It is difficult to determine what the negative test means; however, anergy tests do not have enough data to support their use. As was mentioned before, a patient can have specific anergy against PPD but still respond to other antigens. A positive reaction to antigens in the anergy test may give false assurance that the negative reaction to PPD is truly negative. So, in the end clinicians should only order PPD tests for TB screening and skip the anergy testing due to the lack of data supporting its use and the new CDC guidelines. It is best to just look at the PPD test results, physical exams, and other lab diagnostics when determining the patient’s risk and his or her best options for chemoprophylaxis.

**PHOSPHATE-BINDING AGENTS USED IN THE TREATMENT OF HYPERPHOSPHATEMIA**

**Introduction**

Hyperphosphatemia, defined by serum phosphate levels greater than 5 mg/dl (normal range 2.5-4.5 mg/dl), is a serious electrolyte abnormality that is associated with increased morbidity and mortality. Studies conducted by the US Renal Data System report that patients found with phosphate levels greater than 6.5 mg/dl have a 27% higher mortality risk than patients with levels ranging between 2.4 to 6.5 mg/dl. Over time, increased phosphate levels can lead to secondary complications affecting many of the major organs, as well as the skeletal system. Hyperphosphatemia stimulates the secretion of parathyroid hormone (PTH), which alters the balance of bone formation leading to skeletal abnormalities. In addition, elevated PTH levels inhibit intestinal calcium absorption, which along with elevated phosphate levels, promotes the deposition of calcium phosphate precipitates in the vasculature of the heart, lungs, kidney, as well as periarticular, cutaneous, and subcutaneous tissues.
Table 1: Guidelines for determining a positive tuberculin skin test reaction.

<table>
<thead>
<tr>
<th>Reaction ≥ 5 mm of induration</th>
<th>Reaction ≥ 10 mm of induration</th>
<th>Reaction ≥ 15 mm of induration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV positive patients</td>
<td>Recent immigrants (&lt; 5 years) from high-prevalence countries</td>
<td>Persons with no risk factors for TB</td>
</tr>
<tr>
<td>Recent contacts of TB case patients</td>
<td>Injection drug users</td>
<td></td>
</tr>
<tr>
<td>Fibrotic changes on chest radiograph consistent with prior TB</td>
<td>Residents and employees* of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS), and homeless shelters</td>
<td></td>
</tr>
<tr>
<td>Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥ 15 mg/d of prednisone for 1 month or more)</td>
<td>Mycobacteriology laboratory personnel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders, other specific malignancies, weight loss of ≥ 10% of ideal body weight, gastrectomy, and jejunointestinal bypass</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children younger than 4 years of age or infants, children, and adolescents exposed to adults at high risk</td>
<td></td>
</tr>
</tbody>
</table>

*For persons who are otherwise low risk and are tested at entry into employment, a reaction of ≥ 15 mm induration is considered positive.

Table 2: Patient Characteristics Causing False-Negative Results.

- Infections
  - Viral (measles, mumps, chicken pox, HIV)
  - Bacterial (typhoid fever, pertussis, overwhelming tuberculosis, tuberculosis pleurisy)
  - Fungal (South American blastomycosis)
- Live virus vaccinations (measles, mumps, polio, varicella)
- Metabolic disturbances (chronic renal failure)
- Low protein states
- Diseases affecting lymphoid organs (Hodgkin’s disease, lymphoma, chronic leukemia, sarcoidosis)
- Drugs (immunosuppressive agents)
- Age (newborns and elderly)
- Stress (surgery, burns, mental illness, graft-versus-host disease)

Much of the mortality associated with hyperphosphatemia results from the cardiac insufficiencies caused by this atherosclerotic process. Acute and chronic renal failure are the 2 most common etiologies of this electrolyte abnormality. It has also been associated to a lesser degree with disorders such as rhabdomyolysis, acromegaly, tumor lysis syndrome, hemolysis, malignant hyperthermia, hyperparathyroidism, and bowel infarction. Phosphorus is one of the essential components of all organ systems as it is the major intracellular anion found attached to lipid, sugar and protein structures. It also plays a vital role in various pathways including the generation of high-energy compounds (adenosine triphosphate), the regulation of the clotting cascade (activation of factors V and X), the activation of coenzymes and the formation of 2-3 diphosphoglycerate (2-3DPG), a major factor in systemic oxygen supply. The approximate amount of phosphorus found
in an average 70-kilogram adult, ranges between 500 to 800 grams. Of this, 85% is stored in the skeletal system, 14% is available to the soft tissues and viscera and less than 1% is found in the extracellular fluid. Although the recommended daily allowance (RDA) of phosphorus is 800 mg, the average daily intake using a typical Western diet can range between 700 to 1400 mg. Healthy patients and those with slight renal insufficiencies can properly eliminate an excessive phosphate intake. The risk for developing hyperphosphatemia does not come into play until renal function becomes severely depressed with glomerular filtration rates of less than 25 to 30 ml/min. Therefore, strategies for the prevention and treatment of hyperphosphatemia are crucial for optimizing the quality of life in patients with renal failure.

In October 2003, Kidney Disease Outcomes Quality Initiative (K/DOQI) published new clinical practice guidelines specifically addressing the evaluation of serum phosphate levels, restriction of dietary phosphorus, and the use of specific phosphate binders in patients with chronic kidney disease. These guidelines are more stringent then previous practice recommendations and specifically state that patients with chronic kidney disease should have a serum phosphate level no greater than 4.6 mg/dl and patients on hemodialysis or peritoneal dialysis should have serum phosphate levels maintained between 3.5 to 5.5 mg/dl. Additionally, the guidelines address the restriction of dietary phosphorus to 800 to 1,000 mg/day in patients with elevated serum phosphate levels. Unfortunately, it is often difficult to reduce phosphorus intake without also reducing intake of essential proteins, thereby limiting the effectiveness of dietary restriction.

Currently, the most effective method of phosphate elimination lies with a class of drugs called the phosphate binders. Although, to date, no specific product has been shown to have an outstanding profile, this class of drugs represents the best chance of reducing morbidity and mortality in patients with hyperphosphatemia. Several classical phosphate binders have been used including the phosphate binding salts of calcium, aluminum, and magnesium. More recently, sevelamer (Renagel®) was introduced as an effective calcium-free, aluminum-free, and magnesium-free phosphate binder. All phosphate binders are generally taken with meals and are administered up to 3 times daily. The K/DOQI guidelines recommend that calcium-based phosphate binders be used as initial therapy followed by calcium-aluminum-magnesium-free products such as sevelamer. If calcium-based phosphate binders are used, the new guidelines recommend that the serum calcium-phosphate product should now be maintained at <55 mg²/dL². Additionally, aluminum-based products are only recommended as short-term therapy (4 weeks) and for 1 course only. Finally, magnesium-based phosphate binders are rarely used and should be avoided due to their toxicity profile. Table 1 summarizes the currently recommended products used for the treatment of hyperphosphatemia.

Calcium
Calcium containing salts are relatively inexpensive, well-tolerated, phosphate binders that have also been shown to reduce PTH levels. Three forms are more commonly used. Calcium carbonate (ex. Os-cal®, Tums®) consists of 40% elemental calcium and these products come in tablet, capsule, powder and suspension forms. Efficacy of phosphate binding capacity may vary between products of this form and carbonate-based products show best activity in an acidic environment. Patients with renal insufficiency tend to have impaired gastric acidification and may have decreased phosphate binding. Calcium acetate, on the other hand, is soluble at a neutral pH and maintains binding activity. The acetate form (ex. Phos-Lo®) is made up of 25% elemental calcium and has comparable efficacy to calcium carbonate, but with only half the total amount of calcium per dose. The third form used, calcium citrate (ex. Citracal®), contains 21% elemental calcium, but requires doses similar to calcium carbonate. Calcium citrate can also enhance the absorption of aluminum products and thus should not be used concomitantly with aluminum binders, some antacids, and sucralfate. Gastrointestinal symptoms are common side effects for all calcium products. Patients may suffer from changes in bowel habits, vague abdominal discomfort and dyspepsia. Constipation is more frequently seen with calcium carbonate than with calcium acetate. With prolonged use of all calcium salt products, hypercalcemia, as well as a secondary hyperparathyroidism, may develop and be severe enough to necessitate that the treatment of hyperphosphatemia be switched to aluminum binders temporarily. Of the calcium binders mentioned, calcium acetate has the lowest and citrate has the highest incidence of hypercalcemia, making calcium citrate the less popular option of the three. Other calcium products, such as calcium ketoglutarate and calcium alginate have also been shown to be effective phosphate binders, although they are currently not used for treatment in the United States.

Aluminum
Aluminum containing salts were among the first phosphate binders used to treat hyperphosphatemia in patients with end stage renal disease, but are now considered to be third-line agents. Currently available formulations include aluminum hydroxide (ex. AmphoGEL®, AlternaGel®) and aluminum carbonate (ex. Basaljel®). When complexed with phosphate at any pH, the aluminum salt can form an insoluble precipitate that is not easily absorbed into the system assuming adequate renal perfusion. For patients with renal dysfunction, significant amounts of aluminum can be retained in the body and have been known to lead to toxic levels causing osteomalacia, bone and muscle pain, an iron-resistant microcytic anemia, and neurological abnormalities. Patient populations most at risk for developing aluminum toxicity include those with diabetes, history of parathyroidectomy, anuria, or failed renal
transplant. If necessary, aluminum binders can be used for severe cases but only on an acute basis with plasma aluminum levels being drawn each month. Long-term treatment with aluminum containing phosphate binders is not recommended.

Sevelamer
A novel phosphate binder called sevelamer (Renagel®) was approved as a safe and effective alternative to the classic options discussed above. This treatment is unique in that it is a water absorbing, nonabsorbed hydrogel-cross-linked polyallylamine hydrochloride that is also calcium, aluminum, and magnesium free. Sevelamer binds phosphates through ion exchange and hydrogen bonding and is most effective at neutral pH. Studies show that sevelamer is as efficacious as calcium carbonate at treating hyperphosphatemia. It also has the beneficial ability to reduce both total and LDL cholesterol levels and is therefore also associated with less coronary and aortic calcification. Although reported side effects are minimal, it has been shown to cause diarrhea and nausea. The most significant drawback of this treatment, which limits its almost ideal profile, is its high price. Compared to calcium products, sevelamer can cost almost 4 times more, with daily treatment ranging around $8.

Conclusion
The treatment of hyperphosphatemia remains challenging for health professionals, even today. Although there are several viable options for treatment, each binder also has disadvantages that limit its use. Calcium salts are efficacious, inexpensive options for patients suffering from elevated phosphate levels unless treatment becomes limited by hypercalcemia. Aluminum binders are useful for patient’s suffering from hypercalcemia although they put patients at risk for associated toxicities. Finally, sevelamer is an equally efficacious and safe option; however, cost limits its use. Fortunately, new treatments for hyperphosphatemia continue to be in development. Currently lanthanum carbonate and cross-linked iron dextran have shown promising results and hopefully may prove to be safe and effective treatments for patients with hyperphosphatemia.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Potential Problem</th>
<th>Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>U (for unit)</td>
<td>Mistaken as zero, four or cc.</td>
<td>Write “unit”</td>
</tr>
<tr>
<td>IU (for international unit)</td>
<td>Mistaken as IV (intravenous) or 10 (ten).</td>
<td>Write “international unit”</td>
</tr>
<tr>
<td>Q.D., Q.O.D. (Latin abbreviation for once daily and every other day)</td>
<td>Mistaken for each other. The period after the Q can be mistaken for an “I” and the “O” can be mistaken for “I”.</td>
<td>Write “daily” and “every other day”</td>
</tr>
<tr>
<td>Trailing zero (X.0 mg), Lack of leading zero (.X mg)</td>
<td>Decimal point is missed.</td>
<td>Never write a zero by itself after a decimal point (X mg), and always use a zero before a decimal point (0.X mg)</td>
</tr>
<tr>
<td>MS MSO₄ MgSO₄</td>
<td>Confused for one another. Can mean morphine sulfate or magnesium sulfate.</td>
<td>Write “morphine sulfate” or “magnesium sulfate”</td>
</tr>
<tr>
<td>µg</td>
<td>Mistaken for mg (milligrams) resulting in one thousand-fold dosing overdose.</td>
<td>Write “mcg”</td>
</tr>
<tr>
<td>Nitro drip</td>
<td>Confused for one another. Can mean nitroglycerin or nitroprusside.</td>
<td>Spell out “nitroglycerin” and “nitroprusside”</td>
</tr>
</tbody>
</table>

Table 1. Phosphate-Binding Agents Used in the Treatment of Hyperphosphatemia.

<table>
<thead>
<tr>
<th>Agents*</th>
<th>Brand Names</th>
<th>Doses†</th>
</tr>
</thead>
<tbody>
<tr>
<td>calcium carbonate (40% calcium)</td>
<td>Os-cal®, Tums</td>
<td>500 to 1000 mg TID</td>
</tr>
<tr>
<td>calcium acetate (25% calcium)</td>
<td>Phos-Lo®</td>
<td>2 to 6 tablets TID</td>
</tr>
<tr>
<td>calcium citrate (21% calcium)</td>
<td>Citracal®</td>
<td>500 to 1000 mg TID</td>
</tr>
<tr>
<td>aluminum hydroxide</td>
<td>Amphogel®, AlternaGEL®</td>
<td>300 to 600 mg TID</td>
</tr>
<tr>
<td>aluminum carbonate</td>
<td>Basaljel®</td>
<td>400 to 500 mg TID</td>
</tr>
<tr>
<td>sevelamer</td>
<td>RenaGel®</td>
<td>800 to 1600 mg TID</td>
</tr>
</tbody>
</table>

Agents in bold are UIC formulary items.

*Not reflective of elemental calcium.
Do these requirements apply to all types of documentation?
As a long-term objective, ambiguous and otherwise dangerous forms of notation should be eliminated from all health care documentation. However, through the end of 2004, the survey and scoring of this requirement will be limited to all handwritten, patient-specific documentation, not just orders. Recognizing that it will take time to deal with inventories of preprinted forms and software that contain the prohibited items, implementation of the “list” for print and electronic media will be encouraged, but not required, i.e., not scored, in surveys conducted through the end of 2004. Thereafter, compliance in all documentation media will be expected and scored.

Does the recommendation for standardizing abbreviations, acronyms and symbols apply only to medication orders?
No. This applies to all clinical documentation, including all types of orders, progress notes, consultation reports, and operative reports.

We will need to be in full compliance with elimination of electronic and handwritten abbreviations by the end of 2004 just in time for our JCAHO visit.

P & T Committee Formulary Action - November 2003

Additions
Dexmedetomidine Injection - restricted to OR
Papain-urea-chlorophyllin Copper Complex Sodium ointment

Line extensions
Scopolamine 1.5 mg transdermal patch
Risperidone 1 mg disintegrating tablet
Ondansetron 4 mg disintegrating tablet

Deletions
Ferrous gluconate 324 mg tablet

New tablet form is now on formulary:
Disintegrating Tablet

Please see below for special handling and administration instructions.

- Oral disintegrating tablets are supplied as blister packs and should not be opened until ready for use.
- Peel back foil to expose tablet; do NOT push the tablet through the foil backing because this could damage the tablet.
- Use dry hands to remove the tablet from the blister unit and immediately place the entire tablet on the tongue.
- The tablet should be consumed immediately once it is removed from the blister unit.
- Tablets disintegrate in the mouth within seconds and can be swallowed subsequently with or without liquid.
- Do not split or chew the tablet.

Authors: Kathy Fit, PharmD candidate
Neera Mahal, PharmD
Connie Larson, PharmD

Reviewers: Dean Schraufnagel, MD
Cheryl Gilmartin, PharmD

Editors: Maria Tanzi, PharmD
Michael Gabay, PharmD, BCPS
Amy Lodolce, PharmD, BCPS