Contrast Media and Nephrotoxicity

Organic radiographic contrast media was first introduced in the 1950s. It has become a very important part of radiologic imaging. There are multiple different types of contrast media, they are all modifications of a 2, 4, 6-tri-iodinated benzene ring. They are classified based on their chemical structure, osmolarity, iodine content and ionization in solution.

Contrast media are commonly used in radiological procedures such as diagnostics (i.e. angiography, CT scan) and treatments (i.e. stenting, embolization). As shown in the Table, there are different types of contrast media.

Table. Types of contrast media.

<table>
<thead>
<tr>
<th>Ionic agents</th>
<th>Low-osmolality dimers (500-1000 mOsm/kg)</th>
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<tbody>
<tr>
<td>High-osmolality monomers (&gt;1000 mOsm/kg)</td>
<td>Diatroizote meglumine/sodium iodipamide lothalame</td>
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<table>
<thead>
<tr>
<th>Nonionic agents</th>
<th>Iso-osmolality dimers (290-300 mOsm/kg)</th>
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<tbody>
<tr>
<td>Low-osmolality monomers (500-1000 mOsm/kg)</td>
<td>Iohexol</td>
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<td></td>
<td>Iodixanol</td>
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The osmolarity value is often expressed in terms of the ratio between the iodine atoms and the number of dissolved particles. The higher the ratio, the better the quality of the x-ray. Studies have shown that the higher the osmolarity, the more cytotoxic the product will be.

Therefore, it is important that physicians and other healthcare providers are aware of the potential adverse effects of contrast media. Adverse reactions include allergic reactions, nephropathy, hypotension and bradycardia, extravasation and drug-induced adverse effects. Allergic reactions, drug-induced reactions and contrast-induced nephropathy will be discussed.

Reactions to contrast media

Allergic reactions to contrast media can occur within 20 minutes of the injection and are independent of the dose administered. These reactions are anaphylactoid, not anaphylactic, because immunoglobulin E is not involved. However, mild symptoms such as urticaria, pruritus, rhinorhea or other moderate to severe symptoms may still occur. Risk factors for these reactions include a previous reaction to ionic or non-ionic contrast media, asthma and/or food or medication allergies. Patients with asthma and food and/or medication allergies have a higher risk of a reaction to contrast media than the general population, 1.2 to 2.5 times higher for asthma and 1.5 to 3 times higher for food/medication allergies.

Contrast media should be avoided, if possible, in those patients with a history of allergic reactions to these products. If a contrast procedure is necessary, patients at risk can be pre-medicated with steroids and/or diphenhydramine to reduce the risk of allergic reactions. Common pre-medication regimens include 2 oral doses of methylprednisolone 32 mg administered 12 and 2 hours before contrast media or prednisolone 50 mg administered 13, 7 and 1 hours before contrast media with or without diphenhydramine 50 mg 1 hour before contrast media. These low-dose steroid regimens are usually well tolerated.
Use of metformin with contrast-media may increase the risk of lactic acidosis from metformin. Metformin should be held for 48 hours after contrast media is administered, or at least until serum creatinine comes back to baseline. If metformin is administered to a patient with renal dysfunction caused by contrast media, it will accumulate and increase the risk of lactic acidosis.

**Contract-induced nephrotoxicity**

Contrast-induced nephropathy (CIN) is the acute deterioration of renal function after parenteral administration of contrast media in the absence of other causes. CIN is defined as an elevation of serum creatinine level of more than 0.5 mg/dL or more than 25% of baseline within 48 hours after contrast media injection. The elevations in serum creatinine peak after 3 to 7 days with return to baseline after 7 to 10 days. In more severe cases, serum creatinine elevations may not peak until 5 to 10 days after the use of contrast media. Renal ischemia and direct toxicity to tubular epithelial cells are thought to be the mechanism by which CIN occurs. Renal ischemia occurs due to decreases in renal blood flow reducing medullary oxygenation. Adenosine and endothelin seem to be involved in contrast-mediated vasoconstriction causing direct toxicity to tubular epithelial cells.

The incidence of CIN in the general population is less than 2%, but increases to less than 20% to 30% in patients with risk factors such as pre-existing renal insufficiency, diabetes, heart failure (NYHA class III/IV) and advanced age (>75 years of age). Other risk factors of CIN include anemia, dehydration, hyperuricemia, concomitant use of nephrotoxic drugs (e.g., aminoglycosides, NSAIDs), and high volumes of contrast media for a single study or more than 1 dose for multiple studies in a short period of time. CIN has been associated with increased morbidity, extended length of stay in the hospital, and increased healthcare costs. Patients undergoing percutaneous coronary interventions have a higher mortality rate if nephropathy develops, possibly because most of these patients have pre-existing renal insufficiency. It is also important to keep in mind that the number of angiographies and CT examinations performed is increasing and higher doses are being administered to sicker and older patients.

The type of contrast media may also influence the risk of CIN. Some studies have shown that there is no difference in the toxicity between low-osmolarity and high-osmolarity media, but other studies have concluded that using low-osmolarity products in renal insufficiency alone or combined with diabetes provides a much lower risk of nephrotoxicity. However, other studies have demonstrated that iso-osmolar contrast media may be less nephrotoxic than low-osmolar; more studies need to be conducted to confirm these differences.

**Prevention of contrast-induced nephropathy**

There is some evidence that periprocedural hydration and some drugs may prevent nephrotoxicity caused by contrast media. Common preventative therapy include sodium bicarbonate infusion or N-acetylcysteine. N-acetylcysteine offers some advantages such as a low side effect profile, cost and positive results shown in randomized trials. This medication along with hydration has been reported to significantly reduce CIN in high-risk patients. However, results have not been consistent in published clinical trials. This may be due to differences in doses, procedures, and volumes/frequency of contrast media, and inclusion criteria used. The N-acetylcysteine regimen most commonly recommended includes 4 doses of 600 mg each, given as 2 doses before and 2 doses after the procedures. Some physicians prefer the more traditional hydration approach with normal saline or isotonic sodium bicarbonate. In one trial with 137 patients, hydration with sodium bicarbonate resulted in a lower incidence of CIN compared to saline hydration (1.7% vs. 13.6%). Other studies have examined the use of intravenous mannitol, furosemide, dopamine, IV theophylline, fenoldopam or bosetan, but these approaches have generally been shown to be non-superior to hydration with normal saline.

**Joint Commission requirements**

According to the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), diagnostic and contrast agents used to diagnose conditions are considered medications. As such, contrast media are subject to the standards for medication management that have been set forth by the Joint Commission regarding patient-specific information, selection and procurement, ordering and transcribing, preparing and dispensing, administration, monitoring, and evaluation of medications at healthcare institutions.

**UIMCC Guideline for contrast-induced nephropathy**

In order to improve safety of medication use at the Medical Center, Discern Adverse Drug Event (DADE) alerts have been built in the electronic medical record (EMR) by the Clinical Decision Support Committee. These are real-time alerts that warn the clinician of a potential drug event during the medication ordering process. Select DADE alerts are designed to provide an override alert printouts in the pharmacy, when a medication is ordered after the DADE alert. These DADE overrides are followed up by a pharmacist.

There are 5 reasons that could trigger a DADE alert after a clinician orders contrast media for a patient: no prior creatinine value and creatinine pending; no prior creatinine value and no creatinine pending; no recent assessment of renal function with last creatinine abnormal (Cr >1.5 mg/dL and/or CrCl < 45 ml/min); no recent assessment of renal function with last creatinine clearance abnormal; renal insufficiency.

More specific to nephropathy, a Medical Center clinical care guideline (Refer to UIMCC Intranet Homepage - Clinical Care Guidelines for complete details) was developed on the prevention of CIN based on literature review. The guideline
Complications of pertussis in adolescents and adults include pneumonia, hospitalization, rib fractures, and, rarely, seizures and encephalopathy. The early treatment of pertussis with macrolide antibiotics is quite successful, however, a late diagnosis of the disease increases the risk for a pertussis outbreak. Therefore, prevention through vaccination is the best treatment.

Vaccine recommendations

Diphtheria, tetanus, and acellular pertussis (DTaP) is an intramuscular vaccine indicated for children less than 7 years of age. All children starting at 2 months of age need to receive a total of 5 doses of DTaP; the last dose is recommended to be administered at 4 to 6 years of age.

Considering the increased risk of infection among adolescents and adults, 2 formulations of pertussis vaccine were approved by FDA in spring 2005 for routine use in patients between the ages of 11 and 64 years. Boostrix and Adacel (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed or Tdap are both indicated as active booster vaccines for use in adolescents (11 to 18 years of age); Adacel is also approved for use in adults up to 64 years of age. In addition to adolescents, adults that come in contact with children less than 12 months old are recommended to be vaccinated as are health care professionals who come in direct contact with patients. Full recommendations for the use of Tdap are available at the CDC website (www.cdc.gov/nip/recs/provisional_recs/tdap-preg.pdf and www.cdc.gov/nip/vaccine/tdap/tdap_adult_recs.pdf).

The main difference between adult/adolescent formulations and child formulations are the lower dose of diphtheria toxoid and lower quantity of pertussis antigens. Both Boostrix and Adacel are administered as a single intramuscular injection of 0.5 mL. Some of the most common side effects of Tdap include low grade fever, redness or swelling at the site of injection, soreness and tenderness at the site of injection, and headache. Moderate and severe side effects are very rare. Seizure, high fever over 105°F and encephalopathy can be some of these critical side effects. An observation period of 15 to 20 minutes after administration of vaccine is recommended to monitor for adverse reactions. Contraindications for the new pertussis vaccine (Tdap) include all patients with a history of serious allergic reaction (anaphylaxis) to any component of the vaccine. Tdap is also contraindicated in patients with a history of idiopathic encephalopathy within 7 days of administration of a vaccine with pertussis components. Patients with moderate to severe diarrhea, moderate to severe acute illness, moderate otitis media, and moderate to severe vomiting should not get this vaccination until all these symptoms resolve.

Summary

Although vaccination for pertussis is included in recommended immunizations for children, the effect of the vaccine decreases over time, making adolescents as well as
the adult population more susceptible to pertussis. Current recommendations from the CDC include vaccination for adults and adolescents, as well as healthcare workers, at risk for the infection with a newly formulated pertussis vaccine.

Herpes Zoster Vaccine (Zostavax)

Varicella or chickenpox is an infectious disease associated with childhood caused by the varicella-zoster virus (VZV). For most children, the illness lasts about 5 to 10 days, and manifests with a blister-like rash, itching, tiredness and fever. However, upon healing of the rash, the virus remains dormant, residing on clusters of sensory nerves, usually in the spinal dorsal root or cranial nerve ganglia. Latency of the virus can last as long as decades, but when immunity weakens, varicella virons can be activated and migrate to the skin erupting in a rash, known as shingles (herpes zoster). The virus, when reactivated, can also destroy neurons and satellite cells causing pain and neuropathy.

There are an estimated number of 1,000,000 cases of shingles each year in the United States alone. Shingles is more common after the age of 50 and the risk increases with advancing age. Secondary infections of shingles rash by staphylococci or streptococci as well as ocular infections with VZV are potential complications. By far though, the most common complication of shingles is postherpetic neuralgia (PHN), defined as pain persisting greater than 6 weeks. This complication has been reported as lasting longer than a year in 37% of those over 60 years of age with shingles and in 47% of those over 70 years of age. The pain from shingles is not easily controlled and in many cases is refractory to treatment. Current therapy regimens include antivirals (acyclovir, famciclovir, or valacyclovir) combined with analgesics, tricyclic antidepressants, or anticonvulsants. These treatment strategies have demonstrated reductions in signs and symptoms of shingles when administered within 72 hours of rash onset. However, they do not prevent PHN.

Since PHN can be a debilitating complication from shingles, especially for the elderly, efforts have focused on prevention of shingles in populations most at risk. It is postulated that intermittent exposure to VZV may boost one's cellular mediated immunity (including increases in T-cell proliferation), providing protection against zoster. Booster immunizations of the pediatric varicella vaccine have been used, however, this may not be appropriate for all populations. The Food and Drug Administration has approved a new vaccine, Zostavax (Merck & Co) that has been specifically developed for administration in older adults (over 60 years). Zostavax has a 14-fold higher virus content than the pediatric varicella vaccine routinely given. This higher virus content is needed since a higher amount of virus is required for boosting T-cell response in older adults.

Recently the Shingles Prevention Study, which included over 3 years of follow-up, was conducted to determine whether a single subcutaneous 0.65 mL injection of Zostavax would decrease the incidence, severity, or both of herpes zoster and PHN in adults 60 years of age or older. Those enrolled into the study had to have a history of varicella, had to have resided in the continental United States for the past 30 years, and be immunocompetent. The findings showed that the vaccine had reduced the incidence of shingles by 51%, with the total burden of pain and discomfort due to shingles 61% lower than placebo among all vaccinated recipients. One finding of importance was that the incidence of PHN was reduced by two-thirds compared with those receiving placebo. There was a greater frequency of adverse events at the injection site among those in the treatment group than the placebo group, with erythema reported at 35.8% and swelling at 26.2%. Overall, adverse events were similar in both groups with systemic adverse events assessed as vaccine-related occurring more frequently with Zostavax.

Summary

Although shingles is generally a self-limiting illness, it can be associated with significant morbidity, due to complications such as neuropathy, especially in elderly patients. Use of a varicella-zoster vaccine has been shown to reduce the incidence of pain and discomfort following an episode of shingles.

Human Papillomavirus Vaccine

Human papillomavirus (HPV) infection is a common viral infection. The virus can be transmitted through cuts on the skin, through sexual contact, or during childbirth from an HPV-infected mother. Among women, persistent infection with HPV has been identified as a causative factor in cervical cancer. As many as 370,000 new cases of cervical cancer are identified each year, 80% of which occur in developing countries. Central America and Sub-Saharan Africa have the highest rates. Cervical cancer is also the third most common cancer-causing death in women in developed countries. The International Agency for Research on Cancer reported a total of 270,000 deaths due to cervical cancer in 2002. Cervical cancer caused by HPV is a disease of great concern since there is no control to its mode of infection. However, mortality from cervical cancer can be reduced if the cancer is detected early.

Diagnosis

Screening for cervical cancer is generally done using a papanicolaou or pap smear, which can detect abnormal or precancerous lesions on the cervix and changes in cells caused by HPV infection. Women who are sexually active and who do not have regular pap tests, are the ones most at risk for HPV-induced cervical cancer.

Treatment

A new FDA approved vaccine, Gardasil (Merck & Co.), is capable of providing anti-HPV prophylaxis in both women and men and is indicated for prevention of cervical cancer.
and other diseases associated with HPV infection. The indication for the vaccine currently only includes women, age 9 to 26 years of age.

The vaccine is a mixture of 4 virus subtypes—HPV-6, 11, 16, and 18—which are responsible for cervical cancer (types 16 and 18) and genital warts (types 6 and 11). Early clinical trials found the vaccine to result in a 90% reduction in the incidence of persistent infection or disease with HPV 6, 11, 16, or 18 compared to a placebo vaccine. A later trial—FUTURE II—which enrolled about 5500 women followed for 24 months, found the vaccine to significantly reduce the incidence of cervical intraepithelial neoplasia (CIN), genital warts, and vaginal or vulvar intraepithelial neoplasia by 95 to 97% compared to a placebo vaccine. The FUTURE II trial enrolled 12,000 women and also compared the HPV vaccine to placebo. Similar results were reported, with 97% efficacy of the vaccine to reduce the incidence of CIN.

This quadrivalent HPV vaccine gained rapid approval from the FDA. Gardasil, administered as a 3-dose series by intramuscular injection, can not only prevent initial infection with HPV, but can also help individuals already infected with 1 of the 4 HPV-components in the vaccine to not be infected by any of the other 3 HPV-subtypes. The most common systemic adverse reaction from the recombinant vaccine is injection site reactions (pain, swelling and erythema) within 1 week, and post dose fever within 2 weeks. Gardasil is not recommended to women planning a pregnancy within a 30-day period after receiving the vaccine. Patients who have a hypersensitivity reaction to an initial dose of the vaccine should not receive subsequent doses.

Summary
Infection with HPV is a leading cause of cervical cancer. Public education by healthcare providers as well as by the government regarding the risk of HPV and the importance of screening for HPV-related cervical cell changes is critical for reducing the incidence of cervical cancer. The Advisory Committee on Immunization Practices (ACIP) has primarily recommended routine vaccination for girls 11-12 years of age. However, the ACIP recommendation also allows for vaccination of girls beginning at 9 years old as well as vaccination of girls and women 13-26 years old.

Update on Mumps
Mumps is an acute viral infection, caused by the mumps virus of the Paramyxoviridae family, that occurs primarily in school-aged children and adolescents. Individuals with mumps present nonspecific symptoms of myalgia, malaise, and headache. Swelling and tenderness of the salivary glands are the most prominent manifestations of this disease. Mumps occurs worldwide and is most prevalent in January thru May.

The annual incidence of mumps in the United States has declined more than 99% since 1967, with only 266 cases reported to the Centers for Disease Control and Prevention (CDC) in 2001. At present, immunity to mumps among children and most young adults relies on prior vaccination. Although rare, some complications associated with mumps include encephalitis, meningitis, orchitis, oophoritis, spontaneous abortion, and deafness.

Recent outbreaks
In the June 2006 MMWR Early Release report, the Advisory Committee on Immunization Practices (ACIP) updated the criteria for mumps immunity and mumps vaccination recommendations. The update was implemented in response to the most recent outbreak of mumps in 11 states of the United States from January 1 to May 2, 2006, with 2,597 cases reported. Although the source of the outbreak is unknown, the mumps viral strain has been identified as genotype G, the same genotype identified in the 2005 United Kingdom mumps epidemic. This outbreak showed that there are limitations to the 1998 ACIP mumps-containing vaccination recommendations, prompting the ACIP to modify its recommendations for vaccination.

Table. ACIP modified recommendations for mumps vaccination.

<table>
<thead>
<tr>
<th>Acceptable Evidence of Immunity</th>
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<tr>
<td>Documentation of 2 doses of a live mumps vaccine instead of 1 for school-aged children (grades K-12) and high-risk adults.</td>
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<tr>
<th>Routine Vaccination for Healthcare Workers</th>
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<tbody>
<tr>
<td>Two doses of a live mumps vaccine for individuals born during or after 1957 without other evidence of immunity.</td>
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<tr>
<td>One dose of a live mumps vaccine for a person born before 1957 without other evidence of immunity.</td>
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<tr>
<th>For Outbreak Settings</th>
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<tbody>
<tr>
<td>Consider a second dose of live mumps vaccine if affected by the outbreak for children 1-4 years old and low-risk adults.</td>
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<tr>
<td>Two doses of live mumps vaccine are highly recommended for healthcare workers born before 1957 without other evidence of immunity.</td>
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There is no specific treatment for mumps; the mumps vaccine is the key to prevention. Available live-attenuated mumps vaccine include MMRII (measles-mumps-rubella) and ProQuad (measles-mumps-rubella-varicella [MMRV]). MMRV is only FDA approved for children ages 12 months to 12 years. According to the ACIP guidelines, MMRV should not be administered in place of the second dose of MMR unless a dose of a varicella vaccine is also indicated or if no MMR is available at the time the second dose of MMR is necessary. Two doses of the mumps-containing vaccine, each 0.5 mL subcutaneously, should be administered to children. The first vaccination should occur for infants from 12 to 15 months of age. A second dose is recommended when children are between 4 and 6 years old. However, children can get the second dose at any age, as long as the second dose is at least 28 days after the first dose. Anyone 18 years of age or older or who was born after 1956, should get at least 1 dose of the vaccine, unless they have had the disease. However, high-risk adults mainly healthcare workers, college students, and international travelers should receive 2 doses.
Contraindications to mumps vaccines include individuals who have had life-threatening allergic reactions to gelatin, neomycin, or to a previous dose of mumps-containing vaccine. Because mumps vaccines are live-attenuated, immunization must be deferred until a moderate or severe acute illness has improved, pregnancy ends, immunosuppression is resolved (except human immunodeficiency virus), or if the patient recently received antibodies or a blood product. Although some adverse events are reported, mumps is a relatively safe vaccine. Possible reactions after a dose of mumps-containing vaccine include fever, rash, joint symptoms, thrombocytopenia, parotitis, deafness, and in rare cases, encephalopathy. Studies have demonstrated the safety of MMR in children allergic to eggs; thus, they can be vaccinated without prior skin testing.

**Summary**

Although incidence rates for mumps have declined in the United States in the last 4 decades, a resurgence of the disease was recently reported. Healthcare professionals should stay updated on the trend in the mumps outbreak and current vaccination guidelines from the ACIP to prevent further transmission and eradicate any possible casualties.

### P&T Committee Formulary Action

**Additions**
- Perflutren lipid microsphere (Definity®)
  - Restricted to Cardiology for echocardiography
- Trypsin, balsam peru, castor oil (Xenaderm®)
  - Restricted to use for stage II perineal wound

**New Dosage Form, Strength or Product Additions**
- Lamivudine/Zidovudine 150mg/300mg tablet
- Saquinavir mesylate 200mg capsule, 500mg tablet
- Acetaminophen/hydrocodone 325mg/10mg tablet

**Deletions**
- Nystatin tablet
- Triple dye
- Tetracycline 500mg capsule
- Sulfacetamide 10% ophthalmic solution
- Flutamide

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