

# Pediatric Pharmacotherapy

**A Monthly Review for Health Care Professionals of the  
Children's Medical Center**

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## **Proper Storage of Vaccines to Maintain Potency**

The importance of proper storage conditions for vaccines and other biological medications is often overlooked. Many products, such as the measles vaccine, are inactivated at high temperatures. There is typically little physical evidence of inactivation, making visual inspection of the products an unreliable method of assuring potency. Most currently available vaccines require refrigeration, while some should be frozen until use. These storage requirements must be adhered to from the time of manufacture to the administration to the patient, a process often referred to as maintenance of the "cold chain". Standards of practice for the storage of vaccines have been established by organizations such as the World Health Organization (WHO), the Centers for Disease Control, and the American Academy of Pediatrics [1-3].

### **Guidelines for vaccine handling and storage**

- Designate one person within each clinic or office to
- coordinate storage and documentation of vaccines
- Provide information to all personnel handling vaccines regarding appropriate storage and documentation practices
- Check all vaccine shipments for any evidence of heat damage upon receipt; check cold chain monitor cards if appropriate
- Routinely check all refrigerators/freezers to ensure proper working order
- Place a thermometer in the refrigerator and maintain a daily log of refrigerator temperatures to document compliance with manufacturers' recommendations
- Avoid storing any food in the same area with vaccines
- Store vaccines in an area away from refrigerated/frozen medications to avoid confusion
- Do not store vaccines in the refrigerator door shelf where temperature fluctuations may be greater
- If possible, store bottles of chilled water in refrigerators and ice in freezers to minimize temperature fluctuations in the event of brief electrical power outages
- Perform a monthly inspection of opened and unopened vials for out-of-date vaccines
- When opening or reconstituting a vial, note the date and time it was prepared; check the manufacturer's recommendations for storage of reconstituted vaccines
- Protect vaccines from light, especially MMR
- Perform a "shake test" for products containing tetanus toxoid; if the product has been allowed to freeze, an insoluble precipitate will form in clumps that cannot be dissolved with vigorous shaking of the vial

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Although these guidelines have been widely publicized, compliance in actual practice remains less than optimal. We tend to think of difficulty in maintaining the cold chain as a problem of developing nations<sup>4</sup>; however, current research has shown this to be a

concern in industrialized countries as well [5-9]. In 1992, Bishai and colleagues (including Dr. Greg Hayden from UVA)[5] visited 50 pediatric offices and clinics in Los Angeles to assess compliance with standard guidelines. Only 16% of the personnel identified as being in charge of vaccine storage were aware of the appropriate temperatures necessary to ensure potency. Recording of refrigerator temperatures was routinely performed in only 20% of the sites evaluated. Nearly one-fourth of the refrigerators inspected by these investigators had inappropriately high temperatures. Similar problems have been identified by other investigators [6-9]. In Wellington, New Zealand [6], a survey of clinics documenting daily refrigerator temperatures found that only 50% of the recordings were within the recommended 2-8 C (35-46 F) range. In South Africa [8], the lack of proper environmental control also was clearly evident. Nearly one-half of the clinics surveyed used the same refrigerator to store both vaccines and food, in contradiction to WHO guidelines. Fourteen percent of the clinics sampled did not even have thermometers to assess refrigerator temperature fluctuations!

The following tables categorize currently used vaccines by recommended storage methods. When stored properly, most unreconstituted vaccine products have a shelf-life of one to two years. In general, live attenuated vaccines are more heat-sensitive than inactivated vaccines [1]. As with all medications, the product information included in the manufacturer's packaging should be referred to for more specific information.

### **Vaccines that should be refrigerated, but not frozen (stored at 2-8 C)**

- BCG
- Cholera
- Diphtheria, pertussis, tetanus (separate or in combination)
- Haemophilus influenzae type b
- Hepatitis A
- Hepatitis B
- Inactivated poliomyelitis
- Influenza virus
- Japanese encephalitis virus
- Measles, mumps, rubella (separate or in combination)
- Meningococcal
- Plague
- Pneumococcal, polyvalent
- Rabies
- Typhoid

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### **Vaccines that should be frozen (stored at -15 C)**

- Oral poliomyelitis
- Varicella (store diluent at room temperature or refrigerate)
- Yellow fever

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Even with optimal compliance with storage guidelines, occasional problems may occur. A mechanical failure or electrical power outage may jeopardize the potency of a vaccine supply. The decision to continue to use a vaccine under these conditions depends upon the product's stability. Frozen vaccines should be discarded if there is evidence of thawing. Some refrigerated vaccines, however, may be salvaged. The following table lists the length of time that common vaccines may be stored at room temperature without affecting potency (table adapted from information provided by Anne E. Hendrick, Pharm.D. of the UVa Drug Information Center, Lederle-Praxis Biologicals, and SmithKline Beecham Pharmaceuticals)[3,10].

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### **Stability of unreconstituted vaccines at room temperature**

- BCG: 6-8 hrs
- DPT (diphtheria, pertussis, tetanus): 72 hrs
- Haemophilus influenzae type b: 24 hrs
- Hepatitis A: 7 days
- Hepatitis B: 48 hrs
- Inactivated poliomyelitis: 4 days
- Influenza virus: 7 days
- Measles: 24 hrs
- MMR (measles, mumps, rubella): 7 days
- Pneumococcal, polyvalent: 30 days
- Rabies: 7 days
- Tetanus toxoid: indefinite
- Yellow fever: 4 days

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Whenever storage conditions are questionable, the vaccine vials should be discarded or returned to the manufacturer for replacement. Although it may appear to be overstated, the importance of ensuring vaccine potency is of great concern. Improved methods of vaccine preparation which would allow the creation of more heat-stable products continues to be a goal of international vaccine development initiatives [11,12]. Unfortunately, the need for strict adherence to maintaining the cold chain remains a part of clinical practice at this time.

### **References**

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3. American Academy of Pediatrics. Active immunization. In: Peter G, ed. 1994 Red Book: Report of the Committee on Infectious Diseases. 23rd ed. Elk Grove, IL: American Academy of Pediatrics; 1994:12-8.
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10. Wiedermann G, Ambrosch F. Immunogenicity of an inactivated hepatitis A vaccine after exposure at 37 C for 1 week. Vaccine 1994;12:401-2.
11. Robbins A, Freeman P, Powell KR. International childhood vaccine initiative. Pediatr Infect Dis J 1993;12:523-7.
12. Lemon SM, Milstien JB. The thermostability of vaccines. Technologies for improving the thermostability of the oral poliovirus vaccine. Internat J Tech Assess Health Care 1994;10:177-84.

## **BUILDING A BASIC PEDIATRIC PHARMACOLOGY LIBRARY**

At this time of year as we send new pediatricians out into practice and welcome our new residents, it seems appropriate to review some basic reference sources for pediatric medication information. The following texts and handbooks are recommended for their unbiased, thorough reviews. For more information, contact the publisher listed or your local bookstore.

### **General Drug Information**

Olin BR ed. Drug Facts and Comparisons. St. Louis: Facts and Comparisons, Inc. 1995.

- covers all drugs, includes information on mechanism of action, pharmacokinetics, adverse effects, and drug interactions
- also includes addresses and phone numbers of drug manufacturers as well as lists of orphan and investigational drugs - loose-leaf binder format, monthly updates
- to order, call 1-800-223-0544

## **Pediatric Drug Information**

- Benitz WE, Tatro DS. The Pediatric Drug Handbook. 3rd ed. Chicago: Year Book Medical Publishers, Inc. 1995.
  - recently updated
  - medications listed by therapeutic class
  - helpful tables
- Taketomo CK, Hodding JH, Kraus DM. Pediatric Dosage Handbook. 2nd ed. Hudson: Lexi-Comp, Inc. 1993.
  - medications listed alphabetically
  - very thorough; adult doses also provided for most drugs
  - used by the UVa pediatrics pharmacy
  - to order, call 1-800-237-2742
- Nelson JD. Pocketbook of Pediatric Antimicrobial Therapy. 10th ed. Baltimore: Williams and Wilkins. 1993.
  - best quick reference for antibiotic dosages
  - contains information in "drug-of-choice" format as well as alphabetical listing
  - inexpensive
  - new edition due later this year

## **Drugs in Pregnancy/Lactation**

Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation. 4th ed. Baltimore: Williams and Wilkins. 1994.

- quarterly updates also available
- (to order, call 1-800-638-6423)

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## **FDA News**

Good news! In an effort to encourage health care professionals to report adverse effects, the FDA has issued a final ruling which bars disclosure of the identities of the reporting individual and the patient by any government agency or product manufacturer. This applies to events related to drugs, biologics, or medical devices reported through the FDA's MedWatch system. The ruling takes effect July 3, 1995. For more information on the MedWatch system, please refer to "A Basic Guide for Reporting Adverse Drug Reactions," Pediatric Pharmacotherapy Volume 1, Number 3, March 1995.

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## **Pharmacology Literature Review**

## **Carbamazepine-associated Stevens-Johnson Syndrome**

While this adverse reaction has been reported in adults, this is the first case occurring in a child. A six year old boy developed symptoms of Stevens-Johnson syndrome while receiving carbamazepine and valproic acid for a mixed-type seizure disorder. Symptoms occurred approximately five weeks after the addition of carbamazepine to his valproic acid regimen. Serum concentrations of the anticonvulsants were within the therapeutic range. Supportive care was provided and the patient experienced a full recovery. Keating A, Blahunka P. Carbamazepine-induced Stevens-Johnson syndrome in a child. **Ann Pharmacother 1995;29:538-9.**

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## **Carbamazepine-Cyclosporine Interaction**

The pharmacokinetics of cyclosporine were studied in six pediatric renal transplant patients. Three of the children were also receiving carbamazepine, while the others served as matched controls. Mean steady-state blood concentrations of cyclosporine per mg of dose received were more than 50% lower in patients receiving carbamazepine. The authors theorize that either induction of cyclosporine metabolism by carbamazepine or a reduction in cyclosporine bioavailability may be responsible for this interaction. Cooney GF, Mochon M, Kaiser B et al. Effects of carbamazepine on cyclosporine metabolism in pediatric renal transplant recipients. **Pharmacotherapy 1995;15:353-6.**

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## **Cost-Benefit of DNase**

Genentech, the manufacturer of DNase (Pulmozyme®), has attempted to identify the potential cost savings associated with the use of their product by patients with cystic fibrosis. The authors prospectively documented the health care expenditures of 968 patients involved in a phase III trial of their product over a 24 week period. The patients receiving DNase required fewer days of antibiotics for respiratory tract infections and spent fewer days hospitalized. The authors estimated a cost savings of \$800 to \$1700 per patient over the 24 week period and concluded that the potential savings should more than offset the cost of the medication for most patients. Oster G, Huse DM, Lacey MJ et al. Effects of recombinant human DNase therapy on healthcare use and costs in patients with cystic fibrosis. **Ann Pharmacother 1995;29:459-64.**

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## **HIV in Children**

While it may not offer any new information to those practicing in the area of pediatric immunology, this article provides a brief summary of current therapies

that may be useful for general practitioners. Several clinical trials of antiviral therapies in children are reviewed by the authors. In addition, dosage guidelines and adverse effects of these therapies are presented. A brief summary of investigational agents is also provided. The remainder of the article is devoted to therapies for prophylaxis against opportunistic infections. Hoernle EH, Reid TE. Human immunodeficiency virus infection in children. **Am J Health-Syst Pharm** 1995;52:961-79.

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### **Renal effects of NSAIDs and Acetaminophen**

It is estimated that approximately 5% of all patients taking NSAIDs, including aspirin, will experience adverse renal effects. The author of this review has provided basic background information on the pathophysiology of these adverse effects as well as a summary of published case reports. Acetaminophen remains the author's choice for an OTC analgesic for patients with renal dysfunction. While not focused solely on pediatric patients, this review may be a useful reference tool for all health care professionals. Whelton A. Renal effects of over-the-counter analgesics. **J Clin Pharmacol** 1995;35:454-63.

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### **Formulary Update**

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 5/26/95:

1. Metformin (Glucophage®) was added to the formulary. This is a unique oral antihyperglycemic preparation for the management of non-insulin-dependent (Type II) diabetes. Unlike sulfonylureas, metformin does not produce hypoglycemia or hyperinsulinemia.
2. The following products were added to the formulary based on the recommendation of the antibiotic subcommittee:
3. Varicella vaccine (Varivax®) was added to the formulary. This live virus vaccine is administered to children 12 months of age or older. A single dose of 0.5 ml, given subcutaneously, is used in children less than 12 years of age. Older children and adults should be given two doses separated by 1-2 months. Seroconversion occurs in approximately 97% of patients with detectable antibody levels persisting for at least four years. The most common adverse effects are fever, typically < 102 F, and local reactions.
4. Hepatitis A vaccine (Havrix®) was also added. This vaccine is indicated for children at least two years of age. At this time, it is only recommended for persons at risk for exposure. For children 2-18 years of age, two doses of 0.5 ml should be given one month apart.
5. Rimantadine (Flumadine®) was approved for prophylaxis and treatment of influenza A viral infection in patients unable to tolerate amantadine.



6. The capsule dosage form of ganciclovir (Cytovene®) was added. The parenteral dosage form is already on the formulary.
7. Capsular polysaccharide parenteral typhoid fever vaccine Typhim Vi®) was also added. This preparation is associated with fewer adverse effects than the older parenteral preparation and unlike the oral live vaccine, it can be used in immunocompromised patients.

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