

Health Matters October/November 2006; Volume 1, Issue 4

“Wait and See” approach for Otitis Media by Fred Aziz

A recent study questions the necessity of antibiotics in the treatment of otitis media. Acute otitis media (AOM) is a common diagnosis for children. Treatment of AOM accounts for an estimated 15 million antibiotics prescriptions written per year in the United States.¹ As worldwide antibiotic resistance increases, due to the widespread antibiotic use, one must always question the use of antibiotics in common self-limiting infections. Currently, guidelines recommend the use of medications for pain, and depending upon the situation, possibly an antibiotic.² It is recommended that patients, under 2 years of age diagnosed with AOM, start a 10-day course of antibiotic therapy.² Ongoing research is examining the need for routine antibiotic use for treating AOM, as compared to a “wait-and-see-prescriptions” (WASP) approach to treatment.¹

Yale-New Haven Hospital conducted a study focused on 2 forms of prescribing by pediatric emergency room physicians.¹ After an AOM diagnosis, patients were either give a “standard prescription” (SP) or a WASP. Caretakers of patients receiving the standard prescription (mostly amoxicillin

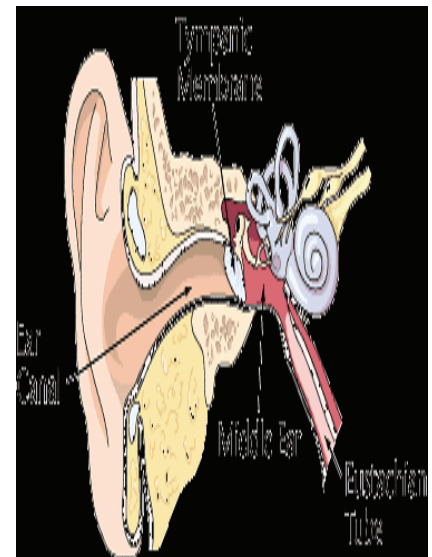
80-90mg/kg/day) were told to fill the antibiotic prescription and administer it starting the day of the office visit.¹ Caretakers of the patients put on WASP were also given a prescription but told not to fill the antibiotic prescription unless your child either is not better or is worse 48 hours after the office visit. Both groups received complimentary bottles of ibuprofen suspension (100mg/5ml) and antipyrine/benzocaine otic drops (54mg/14mg/drop). Instructions for the use of the ibuprofen (10mg/kg per dose every 4-6 hours as needed for pain or fever) and use of otic drops (4 drops in affected ears every 2 hours as needed for pain) were written on discharge forms and were reviewed orally with each patient.

Of the 776 patients diagnosed with AOM, between July 2004 and July 2005, 283 were randomized (145 to SP and 138 to WASP). Prescriptions were not filled for 62% and 13% of patients in the WASP and SP groups, respectively. For children younger than 2 years, 47% of parents did not fill the prescription in the WASP group compared with 5% in the SP group. The patients in the WASP group, whose parents filled the prescription, reported it was due to fever (60%), otalgia (34%), or fussy behavior (6%). Otalgia is defined as having pain of the ear. The only significant difference found between the 2 groups was that otalgia lasted 0.4 days longer in the WASP arm compared to SP, a finding consistent with previous reports that immediate use of an antibiotic shortens the duration of otalgia.

This trial demonstrated that WASP is a successful treatment option in children between 6 months and 12 years of age diagnosed as having AOM.¹ Infants less than 6 months were not included in the study. Overall, the WASP reduced the use of antibiotics by 56% in children between 6 months and 12 years of age.¹ Refraining from immediate use of antibiotics may provide a greater advantage due to decreased cost, prevention of adverse effects, and preventing resistance of commonly used antibiotics.

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Congestive Heart Failure and Thiazolidinediones: a Review

by Leigh Maine

Thiazolidinediones (TZD), also known as *glitazones* are a commonly used class of antidiabetic drugs. The class is comprised of rosiglitazone (*Avandia*) and pioglitazone (*Actos*). A third member of the drug class, troglitazone (*Rezulin*), was removed from the market in 2000 due to reports of hepatotoxicity.¹

Researchers are now questioning the relationship the thiazolidinediones have with congestive heart failure. In 2005, Dormandy, et al., conducted the PROactive trial in order to assess the effects of pioglitazone on macrovascular morbidity and mortality in high-risk patients with type 2 diabetes.² After 3 years of pioglitazone therapy patients had a 16% lower combined risk of heart attack, stroke and premature death (P = .027) compared with patients taking placebo. However in that same study, it was revealed that there was an increased incidence of reported heart

failure (11% in the pioglitazone group versus 8% in the placebo group, P<0.0001).² It is clear that thiazolidinedione therapy is beneficial in insulin sensitivity and macrovascular morbidity and mortality, but patients with CHF risk complications with the therapy.

Earlier this year, the product labeling for rosiglitazone was changed to warn of the increased risk for cardiovascular events associated with its use in patients with New York Heart Association Class I and Class 2 cardiac status.¹ Pioglitazone labeling has not been changed, but it is important to consider these warnings as a potential class effect and use caution with administration of the entire class.

In response to the labeling change, the American Diabetes Association and the American Heart Association have produced recommended guidelines for the use of thiazolidinediones in CHF. The following guidelines should be utilized before administering thiazolidinedione therapy:^{3,4}

- Before prescribing a TZD, a thorough history and physical examination for risk factors, such as a previous myocardial infarction or significant valvular disease, that could predispose a patient to congestive heart failure should be performed.

- Other medications should be considered, such as vasodilators, that may contribute to fluid retention. Agents such as nonsteroidal anti-inflammatory drugs should be discontinued if possible.

- Peripheral edema is not a contraindication for TZD use, but it should be monitored during TZD therapy.

- After starting a TZD, patients should be instructed to report a weight gain of more than 3 kg, new pedal edema, dyspnea, or fatigue. Side effects may occur around 4 to 8 weeks after starting the drug.

- In patients without known heart disease but with one or more cardiac risk factors, the TZD should be started at a low dose and increased cautiously, with special attention to fluid overload.

- TZDs may be used with close supervision in patients with mild to moderate congestive heart failure (NYHA class I or II). However, one should start with a very low dose,

and increase it slowly and cautiously, watching for significant weight gain (> 6 pounds or 3 kg within a few weeks), pedal edema, or acute onset of shortness of breath.

- TZDs should be avoided in patients with moderate to severe heart failure (NYHA class III or IV).

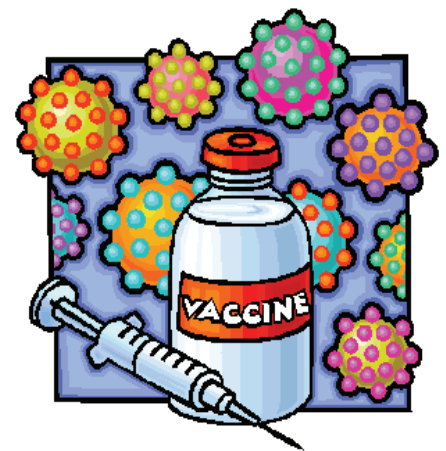
- If fluid retention develops during TZD therapy, especially in the first few months of treatment, congestive heart failure should be investigated with an electrocardiogram or echocardiogram, and, if needed, confirmed with a serum BNP measurement.

- If a patient treated with a TZD has evidence of fluid retention, the TZD dosage may be lowered or discontinued. Adding an angiotensin-converting enzyme inhibitor with or without a thiazide diuretic may reduce edema.

- Discontinuation of TZD treatment should be considered for any patient who develops congestive heart failure. After it is discontinued, symptoms of volume overload usually resolve quickly with short-term diuretic therapy.

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2006 CDC updates on influenza by Anh Thu Diep

In 2006, the Advisory Committee on Immunization Practices (ACIP) recommends six principle changes or updates on influenza.

Recommendations for children aged 24–59 months and their household contacts and out-of-home caregivers.

- All healthy children aged 24 – 59 months and their caregivers should be vaccinated against influenza. In 2005, recommendations were only available for children aged 6 months – 23 months, this change extends the recommendations so that all children aged 6 – 59 months receive their annual vaccination.

Recommendations for vaccination between the age of 6 months through 8 years with emphasis on the importance of giving two doses of influenza vaccines for those who were previously unvaccinated.

- Two doses of vaccines should be given to children between the aged of 6 months – < 9 years who have not been previously vaccinated with live, attenuated influenza vaccine (LAIV) or trivalent inactivated influenza vaccine (TIV).
- Children who receive TIV should have a booster dose of TIV given ≥ 1 month after the initial dose and if possible before the onset of influenza season.
- Children who receive LAIV should have a second dose of LAIV given 6 – 10 weeks after the initial dose and if possible before the onset of influenza season.
- Only 1 dose of vaccine is required for this season in those children who for the

first time in the previous season received their first dose of vaccine but did not receive the second dose within the same season.

Advice for health care providers, those planning organized campaigns, and state and local public health agencies.

- To prepare and ensure optimal use of available doses of influenza vaccines, health care providers, those planning organized campaigns, and state and local public health agencies should develop plans to expand communications and services to provide vaccination to more persons than the previous year. In addition, plans should be developed to prioritize and ensure timing of administering influenza vaccine, and guidelines for dealing with situation such as when supplies of vaccine are delayed or reduced due to production.

Remind providers to continue offering influenza vaccines to patients throughout the influenza season.

- ACIP emphasizes the importance to continuing to offer and provide influenza vaccine throughout the influenza season even after influenza activity has been documented in the community. Also, all community vaccinators and public health agencies should plan to schedule clinics that can serve target groups and offer at least one vaccination clinic in December to help extend the routine vaccination season.

Recommend not using amantadine or rimantadine for the treatment or chemoprophylaxis of influenza A in the United States.

- Due to evidence indicating the widespread resistance to these antiviral medications, ACIP recommends that neither amantadine nor rimantadine be used. If antiviral treatment or chemoprophylaxis of influenza is indicated, oseltamivir (Tamiflu) or zanamivir (Relenza) may be prescribed.

The 2006 – 07 trivalent influenza vaccine virus strains are:

- A/New Caledonia/20/1999 (H1N1)-like antigen
- A/Wisconsin/67/2005 (H3N2)-like antigen: manufacturers may use the antigenically equivalent A/Hiroshima/52/2005 virus.
- B/Malaysia/2506/2004-like antigen: manufacturers may use the antigenically equivalent B/Ohio/1/2005 virus.

More information on influenza vaccines can be found on the CDC website at <http://www.cdc.gov>

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Influenza Vaccine Dosage Chart ²

Inactivated, Injectable Influenza Vaccine					
Trade name	Manufacturer	Age Group	Dose/Presentation	Number of Doses	Route
Fluzone	Sanofi Pasteur	6 – 35 months	0.25 mL prefilled syringe	1 or 2 ⁱ	Intramuscular ⁱⁱ
		36 months and older	0.5 mL prefilled syringe		
			0.5 mL vial		
		6 months and older	5.0 mL multi dose vial		
Fluvirin	Novartis Vaccine (formerly Chiron Corporation)	4 years and older	0.5 mL prefilled syringe	1 or 2 ⁱ	Intramuscular ⁱⁱ
			5.0 mL multi dose vial		
Flurarix	GlaxoSmithKline	18 years and older	0.5 mL prefilled syringe	1	Intramuscular ⁱⁱ

ⁱ Children 8 years of age and younger who are receiving influenza vaccine for the first time should receive two doses of the vaccine. Doses of injectable flu vaccine should be administered at least 1 month apart.

ⁱⁱ Children 6 months to 12 months old should be vaccinated in the anterolateral aspect of the thigh. Older children and adults should be vaccinated in the deltoid muscle if muscle mass

Drug-resistant Staphylococcus infections by: Trisha Tom

Antibiotic resistance is among the Food and Drug Administration (FDA) and Center for Disease Control and Prevention (CDC)'s top concerns constituting an escalating threat to public health. Since the 1980s, Methicillin-resistant *Staphylococcus aureus* (MRSA) infections have become endemic to the hospital and prevalent in the community, and without enforced preventative strategies, reports of vancomycin-intermediate *Staphylococcus aureus* (VISA) and vancomycin-resistant *Staphylococcus aureus* (VRSA) infections will increase in incidence. The current drug of choice to treat MRSA is vancomycin. Linezolid, daptomycin, tigecycline, and quinupristin/dalfopristin are possible treatments for VRSA (see Table 1). The major contributing factor for the increasing prevalence of MRSA is uncontrolled transmission. Transmission of resistant *S. aureus* occurs through direct contact, from person-to-person or between people and environmental surfaces and equipment. Studies have shown that especially with proper hand hygiene of health care workers, there is a significant reduction in transmission of resistant *S. aureus*.¹ Appropriate use of antibiotics, especially vancomycin, is also crucial in minimizing resistant *S. aureus*. Situations in which the use of vancomycin is appropriate are: treatment of serious b-lactam resistant gram positive cocci, serious allergies to b-lactam antibiotics, antibiotic-associated colitis unresponsive

to metronidazole or if severe/life-threatening, or prophylaxis for major surgical procedures when penicillin allergy and endocarditis risk factors are present.³

As of May 2006, six cases of VRSA have been identified in the United States.^{2,6} Although this amount seems miniscule, controlling VRSA and preventing its emergence is vital. The third reported incidence of VRSA in 2004 highlighted the failure of several standard automated susceptibility tests to identify VRSA, suggesting that VRSA may possibly escape detection with inappropriate susceptibility testing.² Most VRSA isolates have developed from preexisting MRSA infections.³ According to the CDC, patients are at high risk for VRSA if they have had prior history of MRSA and VRE. One possible mechanism of the emergence of VRSA is the transfer of the vanA gene from VRE into MRSA, creating VRSA.² With limited treatment options for VRSA, it is extremely essential that all cases of VISA/VRSA be rapidly and accurately identified and isolated; and also reported to the CDC.

Currently, an antimicrobial resistance action plan is being established by a federal task force made of representatives from the National Institute of Allergy and Infectious Disease (NIAID), CDC, FDA, the Agency for Healthcare Research and Quality and several other government agencies.⁶ Further, a num-

ber of investigational antibiotics, particularly glycopeptides and cephalosporins, are currently being studied in phase III clinical trials as alternatives to vancomycin to treat resistant *S. aureus*.⁸

- Oritavancin: investigational bactericidal glycopeptides for treatment of skin and soft tissue infections (currently phase III clinical trials)
- Dalbavancin: investigational bactericidal once weekly IV lipoglycopeptide for treatment of MRSA in complicated skin and soft tissue infections
- Telavancin: bactericidal injectable lipoglycopeptide (currently in phase III clinical trials)
- Ceftibiprole medocaril: anti-MRSA cephalosporin in skin and skin structure infections (currently in phase III clinical trials)



Until updated enforced guidelines are initiated to prevent antibiotic resistance and definitive infection-control strategies are established, health care workers and potentially exposed individuals should take the proper precautions to contain drug resistant *S. aureus* infections.

Table 1. Types of *Staphylococcus aureus* infections^{1,5,7,9}

<i>S. aureus</i> resistant infection	Year 1 st reported in the U.S.	Risk Factors	Treatment Considerations
MRSA (methicillin-resistant <i>S. aureus</i>)	1968	<ul style="list-style-type: none"> • underlying health conditions (diabetes, kidney disease) • nursing home resident or prior hospitalization • prior antibiotic use 	<ul style="list-style-type: none"> • IV Vancomycin^b • Trimethoprim/Sulfamethoxazole^a • Doxycycline^a • Linezolid^a • Clindamycin^a (*inducible resistance over time)
VISA (vancomycin-intermediate <i>S. aureus</i>) *vancomycin MIC: 8-16 µg/mL	1997	<ul style="list-style-type: none"> • underlying health conditions (diabetes, kidney disease) • Dialysis • previous MRSA infections (within last 3 months) 	<ul style="list-style-type: none"> • Linezolid (Zyvox®)^a • Daptomycin (Cubicin®)^b: not effective in pneumonia because binds surfactant in lungs • Tigecycline (Tygacil®)^a • Quinupristin/dalfopristin (Synercid®)^a
VRSA (vancomycin-resistant <i>S. aureus</i>) *vancomycin MIC: ≥ 32 µg/mL	2002	<ul style="list-style-type: none"> • catheters (e.g. IV lines) • exposure to vancomycin and other antibiotics 	<ul style="list-style-type: none"> • Vancomycin + β-lactam: may improve clinical outcome according to one study⁹

^abacteriostatic, ^bbactericidal

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Risks of Taking Triptans with SSRIs or SNRIs by: Julie Kim

The Food and Drug Administration (FDA) is advising against prescribing and dispensing certain migraine medications if a patient is already taking a serotonergic antidepressant. The Public Health Advisory, released July 19, 2006, warned patients and health care providers of the increased risks of serotonin syndrome when triptans (5-hydroxytryptamine agonists) are taken during the same course of therapy as SSRIs or SNRIs.² An article was published by the American Academy of Family Physicians advising against the combination in March of 2000, although the FDA did not comment at that time.¹

- Serotonergic antidepressants increase the amount of serotonin within the neuronal synapses. Triptans work essentially as serotonin receptor agonists. The combination of the two medications results in excessive levels of serotonin that may lead to serotonin syndrome. Symptoms of serotonin syndrome include: restlessness, hallucinations, loss of coordination, fast heart beat, rapid changes in blood pressure, increased body temperature, using a triptan with an SSRI or SNRI.
- Discuss the possibility of serotonin syndrome with patients who may use a triptan in conjunction with an SSRI or SNRI.
- Follow patients closely who are using a triptan together with an SSRI or SNRI.
- Ask such patients to seek medical attention immediately if they experience serotonin syndrome symptoms.

The following indicates the generic and brand names of relevant medications:²

SSRIs	SNRIs	Triptans
Citalopram (Celexa®)	Duloxetine (Cymbalta®)	Almotriptan (Axert®)
Escitalopram (Lexapro®)	Venlafaxine (Effexor®)	Eletriptan (Relpax®)
Fluvoxamine (Luvox®)		Frovatriptan (Frova®)
Fluoxetine (Prozac® and an ingredient in Sym-bax®)		Naratriptan (Amerge®)
Paroxetine (Paxil®)		Rizatriptan (Maxalt®; Maxalt MLT®)
Sertraline (Zoloft)		Sumatriptan (Imitrex®)
		Zolmitriptan (Zomig® and Zomig ZMT®)

Health care professionals should take special care to look out for the combination of these two medications that have been prescribed in the past, as well as those newly prescribed. Preventative health care measures, such as educating patients on the types of medication they take and the risks of serotonin syndrome, may also help protect patients from possible complications

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The FDA Cracks Down on Pharmacy Compounding by Jill Kestel

Recently the FDA warned three medical supply companies that they were operating as a manufacturer and not as a pharmacy compounding in request of a physician prescription. These companies have been compounding inhalation solutions and distributing mass quantities all over the country. These compounded solutions are very similar to products such as DuoNeb® and Pulmicort® that are already FDA approved. No actions have been taken yet by the FDA other than to warn these companies of their illegal acts and if they do not change, further unannounced actions will be taken to stop this activity.¹

These companies are in violation of at least three laws, misbranding, non-FDA approved drug distribution, and compounding and dispensing a copy of an already FDA approved drug on the market.^{2,3}

These are violations of sections 201g, 502, and 505 of the Federal Food, Drug and Cosmetic Act (FDCA).⁴

The Food and Drug Administration Modernization Act was signed in 1997, adding section 503A to the Federal Food, Drug, and Cosmetic Act. This section deals with the issues of pharmacists compounding prescription drugs for patients. In 2002 several compounding pharmacies went to court arguing specific points in this act. The Court of Appeals for the Ninth Circuit declared section 503A of the FDCA unconstitutional, claiming that it violates the right to commercial speech. According to section 503A, pharmacists and phar-

macies are not allowed to advertise and promote their compounded medications. The Supreme Court later finalized this ruling by declaring section 503A unconstitutional and therefore, unenforceable. After this ruling the FDA took action to form guidelines for the FDA and for pharmacies to follow in regards to this ruling. It is important to note that these FDA guidelines are not law, but it is what the FDA is looking for and will be following when inspecting pharmacies.⁵

These guidelines from the Compliance Policy Guide focus on the following nine areas:⁵

1. Compounding should only be performed in pursuant of a prescription
2. Drugs that have been removed from the market should not be compounded
3. Using compounding materials that are not FDA approved
4. Obtaining drugs from a manufacturer without a written statement that the drugs are FDA approved
5. Using drugs that are known not to be FDA approved
6. Compounding massive amounts of drugs
7. Compounding drugs that will be sold to a third party for resale
8. Compounding drugs that are already FDA approved and on the market
9. Failing to uphold state laws and regulations regarding compounding

The FDA will allow the state to handle most violations when it comes to compounding in

pharmacies. In situations that arise when pharmacies are operating on a manufacturing level or misbranding takes place, the FDA will most likely step in and handle it themselves. It is important to know and understand compounding laws, regulations, and guidelines for the state in which you are practicing. As the medical field moves towards individualizing therapy for patients and compounding more prescriptions, the more important it is to follow these rules that have been established, not only for legal purposes, but for the safety of patients as well.

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Generic Plavix® Trial Set for January 2007 by Christy Anderson

Plavix® (clopidogrel) is a registered trademark of Sanofi-Aventis, and is the world's best-selling antiplatelet and antithrombotic agent, occupying 30% of its market. Plavix® is used by 48 million Americans and global sales totaled \$5 billion in 2004,¹ but forecasts expect sales to peak in 2011 at \$6 billion.²

Sanofi-Aventis and Bristol-Myers' share sales of Plavix®, and the original patent filed in 1983 that claimed both enantiomers of the compound, and their mixture, expired in July of 2003. In 1989, Sanofi filed another patent claiming only the active (+) enantiomer, which is set to expire in 2011.³ The generic manufacturer, Apotex, now claims they can manufacture and distribute their generic clopidogrel without legal repercussions due to a loophole based on these separate patents.

Earlier, Sanofi-Aventis and Bristol-Myers' agreed to pay a minimum of \$40 million to Apotex to delay selling its drug until 2011. In July of 2006, the State Attorneys General rejected the modified settlement submitted by the companies to the Federal Trade Commission, and Apotex distributed its generic clopidogrel bisulfate 75mg on August 8, 2006.⁴

On August 31, a federal judge blocked the distribution of the generic version at the request of Sanofi-Aventis, citing the company adequately demonstrated that the questions raised by Apotex as to the validity and enforceability of its patent were without substantial merit.⁵ At this trial, Sanofi-Aventis claimed that "allowing Apotex to flood the market with its product and force prices lower would cripple the spirit of drug innova-

tors, jeopardizing future pioneering medical breakthroughs."⁶ Although the judge stopped further distribution of the drug, he did not force Apotex to remove their product already on the market in the U.S. Apotex claims they will immediately appeal the decision and will file an emergency motion with the Court of Appeals for the Federal Circuit to stay the injunction pending the appeal.⁷ In granting the injunction, the Court has required Bristol-Myers' to post a \$400 million bond to compensate Apotex for damages should it prevail in its patent dispute with Bristol-Myers' and Sanofi-Aventis over Plavix® even though Apotex asked for bond to be set at \$4 billion.⁷ A trial to settle patent disputes has been set for January 22, 2007.⁸

Since the judge denied demands by the brand manufacturers to force Apotex to remove its product already sold to U.S. distributors, the American public will find generic clopidogrel available in pharmacies until this supply is gone. Sanofi has not yet determined precisely how much generic product has been shipped to U.S. distributors, but based on available information, it is believed that Apotex has sold sufficient quantities to satisfy all market demand through the end of 2006; while Apotex claims there is a three month supply in the U.S. market.⁹ The trial set in January will determine the products availability in the future.

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Health Matters October 2006; Issue 1, Volume 4

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