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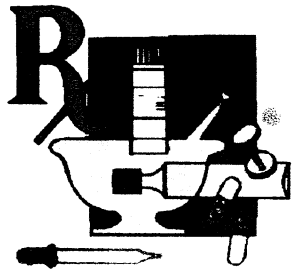

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Upper Gastrointestinal Disorders and the Place of Proton Pump Inhibitors

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The treatment of upper gastrointestinal disorders constitutes a major health expense. In 1998 the Office of Medical Assistance Programs (OMAP) spent $3.7 million on drug treatment of acid related disorders with an increase in the use of proton pump inhibitors (PPIs). This article will discuss the management of common conditions such as non-ulcer dyspepsia (NUD), gastro-esophageal reflux disease (GERD) and peptic ulcer disease (PUD) and will review the place of proton pump inhibitor therapy in the treatment of these conditions.

Dyspepsia may be caused by a number of conditions including peptic ulcer, atypical gastric reflux, non-ulcer dyspepsia, and gastric or esophageal cancer. Failure to establish a diagnosis can result in treatment failures, high recurrence rates, the emergence of bacterial resistant strains, increased health care costs and unnecessary waste of health care resources.

The cause of dyspepsia can be identified by use of a careful medical history, endoscopy and/or serology testing for the presence of *Helicobacter pylori* infection. Early endoscopic examination enables detection of premalignant lesions or early gastric or esophageal carcinoma, duodenal or gastric ulcers and complications of GERD. It is recommended that all patients over the age of 45 years with recent onset dyspepsia be referred for endoscopy.[1,2,3] Gastric malignancy is rare below the age of 45 and patients younger than 45 do not require endoscopy unless they present with sinister signs which could indicate severe underlying disease such as unexplained weight loss, unexplained iron deficiency anemia, recurrent vomiting or frequent NSAID use.[1,2,3] Any patient with severe persistent symptoms not responding to empiric treatment should be referred for endoscopy.[2]

Patients under 45 years of age who are not candidates for initial endoscopy should be tested for evidence of *H. pylori* infection.[1,2,3,4] Carriers of *H. pylori* are 3-10 times more likely to develop peptic ulcer disease and 2-10 times more likely to develop gastric cancer than non-carriers.[5] Non-ulcer dyspepsia and GERD are not thought to be linked to the presence of *H. pylori*.[5] Eradication therapy is recommended if there is documented *H. pylori* infection and peptic ulcer disease is suspected.[1,6,7] A follow up visit is recommended within 4-8 weeks. If symptoms fail to respond, rapidly recur, or alarming features

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Recommendations for Treating Common Respiratory Tract Infections

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Antimicrobial resistance has become a major health care problem in the United States.[1] One of the more disturbing developments during the past 5 to 10 years, has been the rapid emergence of drug-resistant strains of *Streptococcus pneumonia* in community acquired infections.[1] Over-prescribing antibiotics is believed to play a major role in the increased prevalence of antibiotic resistant bacteria.[1] Recent published surveys of primary care physicians reveal that 44% to 75% of adults and children with a diagnosis of the common cold, upper respiratory tract infection (URI) or acute bronchitis, received an antibiotic prescription even though these conditions generally do not respond to antibiotic therapy.[2,3] Similarly, a survey found that although there was concern about the spread of antibiotic resistance, 71% of family physicians and 53% of pediatricians would immediately prescribe antibiotics for infants with scant, green nasal mucopurulent secretions of one day duration.[4] Previous antimicrobial use has been identified as a risk factor for invasive pneumococcal disease with multiple drug-resistant strains.[1] Importantly, evidence indicates that when judicious antimicrobial use is instituted, problems associated with antimicrobial resistance decrease.[1]

The Center for Disease Control and Prevention (CDC) estimates that 50% of the 100 million courses of antibiotic treatments prescribed during office visits each year are unnecessary. In response to the growing problem of antimicrobial resistance the CDC, in collaboration with a variety of medical organizations, has developed recommendations to guide the prescribing of antibiotics for common respiratory tract infections. Patient education materials have been developed to assist clinicians in educating patients about the appropriate use of antibiotics. This article summarizes current recommendations for antibiotic use in a variety of common respiratory tract infections.

Acute Otitis Media

Otitis media accounts for more antibiotic prescriptions than any other condition. It is important to differentiate acute otitis media (AOM) from otitis media with effusion (OME). OME is rarely an indication for antibiotic therapy.[5] Acute otitis media (AOM) is diagnosed by fluid in the middle ear with the presence of specific signs or symptoms of acute, local or systemic illness such as a red tympanic membrane, otalgia or otorrhea, or nonspecific symptoms such as fever. Other signs and symptoms such as rhinorrhea, cough, irritability, headache, anorexia, nausea and vomiting may be present, but are not specific for AOM and are not adequate alone to differentiate AOM from OME.[5]

OME is characterized by fluid in the middle ear with absence of signs or symptoms of acute infection. OME typically follows an episode of treated AOM. Seventy percent of children have a middle ear effusion at 2 weeks, 50% at one month and 10% at 3 months after treatment. Antibiotics are not indicated for OME unless a bilateral effusion persists for at least 3 months and is accompanied by documented hearing loss.[5] The routine of rechecking children at 2 weeks and prescribing a different and often expensive antibiotic when OME is present is discouraged.

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develop, prompt upper endoscopy is indicated.[1,2] No recommendation for the treatment of GERD or non-ulcer dyspepsia can be made at this time.[3,5,8,9] There are several new treatment guidelines available for *H. pylori* eradication.[2,3,6,9]

Non-Ulcer Dyspepsia (NUD)

Up to 60% of patients with dyspepsia have no endoscopic evidence of peptic ulceration or other structural disease other than gastritis. These patients have non-ulcer dyspepsia, or functional dyspepsia.[2,10] The pathophysiology of this condition is poorly understood.[10] Treatment should begin with introduction of lifestyle changes such as smoking cessation, weight loss and avoidance of fatty foods. Simple antacids may be prescribed and any NSAIDS and other provoking agents should be stopped, if possible.

If lifestyle changes and simple antacids do not control symptoms, then a four week trial of antisecretory therapy (e.g. H2 antagonist) is recommended. Generic cimetidine or ranitidine are the most cost-effective options.[2] (See Table 2.) If there is no response to H2-antagonist therapy, cisapride or a PPI may be tried for an additional four weeks.[2] Alternative diagnoses such as biliary disorders should be investigated if there is still no response to therapy.[3] Behavioral therapy, psychotherapy or antidepressants may be beneficial for patients with persistent symptoms although the value of these approaches has not yet been fully established.[2,10]

Gastro-esophageal Reflux Disease (GERD)

GERD is a chronic relapsing condition with a lifetime prevalence of 25-35% for the US population.[11] It can usually be distinguished from other causes of dyspepsia by its classic presentation. The most common symptoms are heartburn which may radiate upwards towards the neck, epigastric or retrosternal discomfort, regurgitation and dysphagia.[11,12] In the absence of these classic symptoms, GERD can be difficult to differentiate. Other presenting symptoms include atypical chest pain, hoarseness, nausea, cough, odynophagia and asthma.[11]

GERD is caused by a number of factors which result in a retrograde flow of gastric contents through the gastro-esophageal junction and a breakdown in the defense mechanisms of the esophagus.[11,12] The duration of exposure of the esophagus to the acid reflux is an important determinant of the severity of injury.[11] Complications of GERD include esophagitis, strictures, ulcers and Barrett's esophagus. Patients with Barrett's esophagus have a 30-125 times greater risk of developing adenocarcinoma of the esophagus.[11]

Some drugs increase the risk of GERD as they lower esophageal sphincter tone, delay gastric emptying or cause mucosal injury (see Table 1). The relationship between GERD and *H. pylori* infection is unclear. Recent observations suggest that GERD may develop following *H. pylori* eradication. Further research is required in this area.[5]

Endoscopy is not sensitive for a diagnosis of GERD alone but may be useful when assessing structural complications of GERD. Twenty-four hour esophageal pH monitoring may be used to establish a diagnosis of GERD particularly if a patient continues with atypical symptoms after a normal endoscopy.[11,12]

The aim of treatment is to minimize exposure of the esophagus to refluxate, allowing the esophagus to heal, thereby alleviating symptoms, preventing complications and maintaining remission.[11] Three strategies may be used in the treatment of GERD; step-up, step down and single agent treatment.[11,12,13] Single agent treatment, the use of the same treatment for all patients, ignores the disease and symptom severity and physiological variations of GERD and is not recommended.[13]

Step down therapy, with PPIs as initial treatment, may be cost-effective in patients with more severe disease (e.g. those with esophageal strictures or documented ulcers) but if used widely could result in unnecessarily high drug costs. Step up therapy may be more cost-effective for patients with less severe disease. It is not clear which approach is best overall (see Figure 1).[13]

Intermittent or maintenance therapy?

Patients with mild to moderate symptoms and infrequent relapses may be treated effectively with intermittent therapy.[12,16] Intermittent treatment of GERD, (the treatment of relapses with either a two to four week course of ranitidine or omeprazole) has been shown to be effective in the management of symptoms in approximately half of patients with uncomplicated GERD.[16] If symptoms recur shortly after treatment is stopped, maintenance therapy may be required.[16]

Patients with severe esophagitis or patients who experience a significant decline in quality of life, may require maintenance therapy from the outset.[17] Patients who require maintenance therapy with PPIs should use the lowest effective dose.[11]

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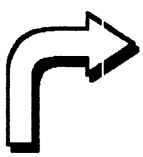
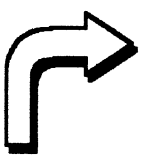
Figure 1: *Stepwise Treatment of GERD*



***STEP THREE*: Proton Pump Inhibitors (PPIs)**

Three PPIs are currently marketed in the US, and pantoprazole may be approved shortly. PPIs have been shown to be more effective than H2 antagonists or cisapride in the maintenance of esophageal healing and are an appropriate choice of therapy for patients with moderate to severe esophagitis.[11, 13, 15] Few patients are resistant to PPIs. If there is a poor response to therapy, the diagnosis should be re-evaluated.[12]



***STEP TWO*: H2 Receptor Antagonists (Preferred) or Prokinetic Agents**

H2 receptor antagonists are effective agents for the treatment of mild to moderate GERD. Treatment results in symptomatic improvement within 8-12 weeks in 50-75% patients with reflux symptoms.[13] Generic cimetidine or ranitidine are the most cost-effective agents. Drug interactions occur more frequently with cimetidine than with other H2 antagonists. The prokinetic agent cisapride has similar efficacy to H2 antagonists in relieving GERD symptoms and healing mild esophagitis. Cisapride may cause cardiac arrhythmia when combined with P450 3A4 enzyme inhibiting agents, with other agents which prolong the QT interval or when prescribed for patients with conditions predisposing to arrhythmia. It should be used with caution and an ECG may be considered prior to initiation of cisapride.[11,12] Metoclopramide, a cost effective prokinetic agent, is associated with a high rate of CNS side-effects including extra-pyramidal effects. It is only effective as short-term therapy and prokinetic effects can abate with long-term therapy.[14]

***STEP ONE*: Lifestyle Changes and Alginate Antacids**

Lifestyle changes which are most likely to be of benefit are a reduction in fat intake, smoking cessation and elevation of the head of the bed.[3,11,13] Epidemiological studies have shown that alginate-antacids are often used successfully by patients with reflux who do not seek medical help.[3,12] A large open trial of patients with mild esophagitis has shown that use of alginate-antacids "on demand" maintained most patients in good clinical remission.[3,12]

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Table 1: Drugs Exacerbating GERD

Drugs affecting lower esophageal sphincter tone	Drugs causing esophageal mucosa injury
Drugs with antimuscarinic effects	NSAIDs
Calcium channel blockers	Potassium chloride
Nitrates	Alendronate
Theophylline	Iron
Alcohol, nicotine, caffeine	Tetracycline

Adapted from: Kinnear M et al. Gastro-oesophageal reflux disease. Pharm J, 1999;263:241-247.

Combination Therapy

Combination drug therapy cannot be justified for most patients with GERD.[11] The use of cisapride with H2 antagonists has been shown to provide better healing rates and symptom relief than either agent alone. However, this combination may lead to an increased incidence of adverse effects and drug interactions, is more costly and is less effective than the use of PPIs alone.[11,12] The combined use of a PPI and prokinetic agent is not usually necessary. If high dose PPI therapy (e.g omeprazole 40mg daily) is ineffective the diagnosis should be reconsidered.[11]

Surgery

Surgery may be considered for younger patients requiring high-dose acid suppression, patients who fail medical therapy or those that develop complications of GERD.[11]

Proton Pump Inhibitors (PPIs)

There are three PPIs currently marketed in the US (omeprazole, lansoprazole and rabeprazole). PPIs are potent antisecretory agents which bind to the gastric proton pump suppressing acid secretion.[11] They are associated with rapid symptom relief, improved maintenance and more rapid healing than H2 antagonists in the treatment of GERD.[11,13,15] It is believed by some that PPIs are too successful as symptom improvers and are too widely prescribed for the treatment of minor symptoms.[18] Their use has escalated despite concerns of high acquisition costs and long term safety.

In 1998, OMAP spent $1.5million on prescriptions for PPIs with usage increasing sharply in the second half of the year. A review of prescriptions for PPI therapy has highlighted many issues which may contribute to unnecessarily high prescribing costs.

- Many patients remained on treatment doses of PPIs, omeprazole 20mg or lansoprazole 30mg daily for long periods, some for 10 months or more. There was low use of once daily omeprazole 10mg and lansoprazole 15mg.

- Many patients who were prescribed a PPI were taking more than one dose per day (e.g omeprazole 10mg bid rather than omeprazole 20mg qd). Prescribing PPIs in this way approximately doubles the costs of these already expensive agents.

New Proton Pump Inhibitors

Rabeprazole (Aciphex®), approved by the FDA this summer, is a partially reversible inhibitor of the gastric proton pump.[19,20] This represents a potentially significant difference to other PPIs, which are irreversible inhibitors. Rabeprazole may have a quicker onset and a shorter duration of action than other PPIs and gastric pH levels return to normal for a few hours each day.[20] It is not yet known whether the effects of rabeprazole and other PPIs will differ as a result of this difference or whether the safety profile of rabeprazole will be improved.[19,20]

Clinical studies have shown rabeprazole 20mg daily for 8 weeks is as effective as omeprazole 20mg daily in the treatment of GERD.[20]

Rabeprazole is metabolized by the cytochrome p450 system. Digoxin levels may be increased by 20% and ketoconazole plasma levels may be reduced with concurrent rabeprazole.[20] Rabeprazole has a much weaker affinity for CYP 2C19 than omeprazole and has not be shown to interact with diazepam, warfarin, theophylline or phenytoin.[19]

Pantoprazole (Protonix®), which may be approved by the FDA later this year, is an irreversible proton pump inhibitor similar to omeprazole and lansoprazole. Clinical studies indicate pantoprazole and omeprazole are equivalent in the treatment of mild to moderate reflux esophagitis.[21] Pantoprazole 40mg daily and omeprazole 20mg daily are also similar in terms of symptom relief and healing rates of duodenal and gastric ulcers.[21] Pantoprazole does not show any appreciable drug interactions.[21]

Neither pantoprazole or rabeprazole appear to add any significant therapeutic advantages to the existing group of PPIs. Further direct comparisons are needed. The costs of these newer agents may ultimately determine their place in therapy.

Conclusion

In order to afford new important therapies we need to target more precisely our use of medicines such as PPIs. There are several effective treatments for uncomplicated GERD and NUD, yet the use of PPIs continues to increase. While they are effective agents and are appropriate choices for the treatment of severe symptoms, their use in less severe disease is often inappropriate and may use unnecessary resources. ◘

Table 2 - Cost Comparison of GERD Step Treatment

	Recommended Dose	*OMAP cost per month*
STEP ONE : Lifestyle changes and alginate -antacids		
Alginate-antacids (Gaviscon®)	10-20ml qid	$20.56-$41.12
STEP TWO : H2 receptor Antagonists. *(Preferred for safety reasons) Equipotent doses of different H2 antagonists are similar in efficacy.* Recommended for intermittent treatment of mild to moderate GERD (including erosive esophagitis). Treat for 8-12 weeks then try withdrawal of medication while continuing Step I management. Use for maintenance of healing of erosive esophagitis if required or if symptoms of GERD recur.		
Cimetidine	400mg qid or 800mg bid for 12 weeks	$21.24-$24.93
Ranitidine	150mg bid	$35.48
	150mg qid (Treatment of erosive esophagitis)	$70.97
Nizatidine (Axid®)	150mg bid	$92.50
Famotidine (Pepcid®)	20mg bid	$94.57
	20-40mg bid for up to 12 weeks (Treatment of erosive esophagitis)	$94.57-$182.77
STEP TWO : Prokinetic Agents For treatment of mild to moderate GERD. Cisapride should be used with caution because of the risk of serious and sometimes fatal side-effects. Cardiac arrhythmia and QT prolongation have been reported and may occur as a result of drug interactions or underlying cardiac disorders. An ECG may be considered before use. Please refer to product information before prescribing. Metoclopromide does not heal esophagitis and is only recommended for short-term use.		
Cisapride (Propulsid®)	10-20mg qid	$82.97-$160.95
Metoclopramide	10-15mg up to qid for 4-12 weeks (Short-term treatment only)	$2.11-$13.16 (qid dosing)
STEP THREE : Proton Pump Inhibitors. *Equipotent doses of different PPIs are similar in overall efficacy.* Recommended for intermittent treatment of moderate to severe esophagitis, poorly responsive to H2 antagonists or prokinetic agents. Use for maintenance of healing of erosive esophagitis if required.		
Lansoprazole (Prevacid®)	30mg daily for 4-8 weeks	$99.71
	15mg daily maintenance therapy	$97.85
Omeprazole (Prilosec®)	20mg daily for 4-8 weeks	$106.42
	10mg-20mg daily maintenance therapy	$95.34-$106.42
Rabeprazole (Aciphex®)	20mg daily for 4-8 weeks	$98.68
	20mg daily	$98.68

Please refer to the article for further information.
Drug prices are from The Red Book, October 1999.
OMAP cost is AWP-11% or the HCFA MAC price of generic drugs

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(References for **GASTROINTESTINAL** appear on page 6)

New Flu Treatment Approved by FDA

By: ***Suhad Searty****, BS Pharmacy Clerkship Student;* ***Helen Varley****, B.Pharm., Dip. Clin. Pharm., MRPharmS.*

Influenza is responsible for 20-25 million physician visits and 20,000 deaths in the US each year.[1] The disease varies in severity. It may keep some people home from school or work, but infection of elderly persons can lead to hospitalization and death. The overall fatality rate of influenza is estimated at 0.01% resulting in tens of thousands of deaths each year.[1]

Zanamivir (Relenza®) is a neuraminidase inhibitor approved by the FDA in July 1999 for the treatment of influenza. It will be available to US prescribers in October 1999. Zanamivir only has FDA approval for the treatment of uncomplicated acute illness due to the influenza virus in adults and adolescents age 12 and over who have been symptomatic for no more than two days. It does not have FDA approval for the prevention of influenza. News stories accompanying the launch of zanamivir have discussed a recent clinical trial where the antiviral agent was used to prevent the spread of influenza. This may have erroneously led patients to believe it is a preventative agent rather than a treatment for influenza.

Treatment of influenza is mostly symptomatic. Amantadine and rimatadine, which are effective against influenza A, can be used for treatment of influenza and if started early can shorten the duration of illness by one day. Zanamivir is currently the only agent with activity against influenza A and B although there is less evidence to support its efficacy against influenza B.[3,4] The overall benefit of zanamivir is described as a reduction in duration of symptoms by one day, although this is dependent on other factors.[3]

Clinical evidence for the efficacy of zanamivir in the treatment of acute influenza in ambulatory patients has not been impressive and in February 1999 an FDA advisory committee voted against the approval of zanamivir. In July 1999 when the product was approved an FDA memorandum stated that zanamivir confers a modest clinical benefit to patients with uncomplicated influenza and that there was no other approved product with efficacy against influenza B.[3]

Clinical studies of zanamivir have shown that:

- Patients are more likely to benefit if treatment is started within 30 hrs of the onset of symptoms.[5]
- There is no benefit seen with zanamivir therapy if patients are afebrile.[4]
- The use of zanamivir does not consistently reduce the risk of complications from influenza.[4]
- No consistent benefit is seen in patients with underlying chronic medical conditions.[4]
- Zanamivir has not been shown to be effective in high risk patients with chronic obstructive pulmonary disease, or asthma. In addition, it is possible that use in these patients may be associated with some risk as it may cause bronchospasm in patients with asthma.[4]
- Patients over 50 years may derive more benefit from treatment. Zanamivir use in elderly patients has not been widely studied.[4]

In summary, clinical studies did not show any great benefit of zanamivir in the treatment of influenza and it is not indicated for disease prevention. For the majority of patients influenza is an acute, brief and self limiting illness which should not require use of zanamivir. If zanamivir is prescribed, patients must be able to use the diskhaler device which delivers the dry powder to the lungs and oropharynx. Treatment is twice daily for five days and is available at a wholesale cost of $44.40 per treatment.

Influenza vaccination continues to be the recommended method for influenza prevention. Annual vaccinations with an inactivated vaccine are 70-90% effective in the prevention of influenza.[3] Antiviral agents amantadine and rimatadine can be used for the prevention and treatment of influenza and are useful in nursing homes in the control of influenza outbreaks.[2] Further information regarding prevention and control of influenza can be found at the CDC website (http://www.cdc.gov/ncidod/diseases/flu/fluvirus.htm) and at the Oregon Health Division website (http://www.ohd.hr.state.or.us/cdpe/acd/docs/influenza.htm)

REFERENCES

1. Drugs 1998;56(4) 537-553
2. N Eng J Med 1997;337:927-928
3. FDA Division Director Memorandum NDA 21-036 Relenza, 7/26/99 http://www.fda.gov/cder/foi/appletter/1999/21036ddm.pdf
4. Relenza Product Label July 1999 http://www.fda.gov/cder/foi/label/1999/21036lbl.pdf
5. N Eng J Med 1997;337:874-880

OMAP Pharmacy Audit Reveals Rule Confusion Re: "Brand Medically Necessary"

OMAP auditors make periodic inspections of pharmacies that dispense to OMAP recipients. Recent audits have revealed some confusion regarding the use of generic products. According to OAR 410-121-0155, "The prescribing practitioner must certify in his/her handwriting that the item is 'brand medically necessary', 'medically necessary' or 'brand necessary' on the face of the prescription. Rubber stamp, initials or a box to check to this effect are unacceptable." This certification must be filed with the prescription within 30 days of filling the prescription and applies to all multisource products. OAR 855-041-0065, of the Board of Pharmacy rules, also require prescriber certification of brand name necessity via phone or in the prescriber's handwriting.

The recent audits revealed widespread dispensing of brand name Lanoxin®, Coumadin®, Compazine® and Lasix® without the necessary certification. OMAP will reimburse for only the generic product price unless there is the appropriate medical necessity certification in the prescriber's handwriting. Pharmacists are encouraged to check with prescribers prior to switching products as it is recognized that there may be variation in products. ◘

1. Oregon State Archives: Administrative Rules
http://arcweb.sos.state.or.us/rules/alpha_index.html

DISPENSING REMINDER FOR COMPOUNDED DRUGS

According to the Oregon Administrative Rules (OAR 410-121-0146), pharmacies will be reimbursed for each component of a compounded prescription if they are billed separately. A dispensing fee is allowed for each billing. Each component must use the actual metric quantity to four decimal places (OAR 410-121-0280).

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The routine use of antibiotics for AOM is controversial.[6] The CDC/American Academy of Pediatrics sponsored expert panel states that antibiotics are indicated for AOM, although the treatment effect is small (80% percent of children recover spontaneously without the use of antimicrobials).[5] A meta-analysis of AOM studies indicated that one child in seven has a more rapid resolution of symptoms with antibiotic therapy.[7] This meta-analysis has been criticized for not including several placebo controlled trials, which would have reduced the estimated clinical benefit.[6] However, in one study, patients with more severe symptoms were more likely to experience treatment failure with placebo than antibiotics.[6] While it is widely believed that antibiotics will reduce the incidence of complications like mastoiditis or meningitis, scientific evidence to support this belief is lacking. Interestingly, in the Netherlands where antibiotics are not routinely prescribed for AOM, only two cases of mastoiditis occurred in 4,860 patients who did not receive antibiotics at initial presentation. Both cases responded to outpatient oral antibiotic therapy.[6] There were no reported cases of meningitis.

It may be reasonable to withhold antibiotics and use symptomatic therapy in carefully selected patients. Children over the age of two that are otherwise healthy with mild uncomplicated AOM, and where follow-up is assured, are reasonable candidates for this approach.[8] The most important risk factors for poor outcome are children younger than 2 years of age, and day care attendance.[6]

Efficacy against *S. pneumonia* is the most important consideration for antibiotic therapy selection for AOM because it is the most common bacterial cause (40-50% of cases), and is least likely to resolve without antibiotics. Episodes of AOM associated with *H. influenza* and *M. catarrhalis* are more likely to resolve spontaneously.[9] Amoxicillin remains the preferred first-line antibiotic for AOM[9] according to the recently published report from the CDC sponsored Drug-resistant *Streptococcus Pneumonia* (DRSP) Working Group. It is highly effective against *S. pneumonia* and produces middle ear fluid levels that remain above the MIC90 for DRSP longer than any other oral antibiotic approved for AOM.[9] The expert panel recommended increasing the dose of amoxicillin from 40mg/kg/day to 80-90mg/kg/day, especially for patients at high risk for DRSP (day care, or antibiotic use in preceding 3 months).[9]

The optimal duration of treatment for AOM is not well established. Traditionally a 10 day course of antimicrobial therapy has been prescribed. This practice is not based on controlled clinical trials and recent studies suggest a 5 to 7 day course of an antimicrobial produces comparable results to longer durations of therapy.[10] This is not surprising since many studies fail to find a difference between antibiotics and symptomatic therapy. One expert panel recommends a 5-7 day treatment for children 2 years or older with an uncomplicated presentation of AOM.[5] Patients with complicated AOM such as perforation of tympanic membrane, chronic or recurrent AOM, craniofacial abnormalities, immunocompromised or children younger than age 2 should continue to receive a longer course of treatment.[5,11]

The use of antibiotics for prophylaxis against recurrent AOM is also controversial. The benefit of prophylactic antibiotics is modest, reducing recurrent episodes by 0.11 per patient per month (about 1 episode/year).[12] Factors associated with the greatest treatment benefit include patients with the highest recurrence rates, sulfisoxazole use, and duration of prophylaxis < 6 months. Prophylaxis may select for colonization or overgrowth of resistant organisms.[12] This has been demonstrated with amoxicillin prophylaxis, but appears less likely with sulfisoxazole. Control re-infection with nonpharmacologic interventions when possible. These include eliminating tobacco smoke exposure, reducing pacifier use, reducing day care attendance and administering influenza vaccine.[12] Antimicrobial prophylaxis (preferably with sulfisoxazole) should be reserved for patients with 3 or more episodes of AOM in 6 months or 4 or more in 12 months, with a duration of therapy not exceeding 6 months.[12]

Sinusitis

Acute rhinosinusitis is a common clinical problem encountered in primary care. While antibiotic therapy may benefit patients with acute bacterial sinusitis, it does not benefit patients with a viral etiology. Viral rhinosinusitis is much more common than bacterial rhinosinusitis. This is especially true in children where one expert panel indicates that viral cases are 20 - 200 times more common than bacterial cases.[13] Thus it is important to limit antibiotic therapy to patients who are most likely to have a bacterial etiology.

Bacterial rhinosinusitis is likely when a patient has persistent nonspecific symptoms (daytime cough and nasal discharge) that don't improve within 10 -14 days, or an URI accompanied by specific and severe signs and symptoms (fever of 39 degrees C or more, facial pain, facial swelling, or dental pain).[13] The presence of mucopurulent rhinitis or thick, opaque, discolored nasal discharge typically occurs during the natural course of uncomplicated viral URI and is not an indication for antibiotics.[13] No single sign or symptom is both sensitive and specific for diagnosing acute bacterial sinusitis. Predictive power is improved by combining signs and symptoms into a single clinical impression. Useful signs and symptoms include "double sickening" (biphasic illness), pain with unilateral predominance, pain on leaning forward, purulent rhinorrhea with unilateral predominance, the presence of pus in the nasal cavity, and maxillary toothache.[14,15]

The bacterial pathogens involved with acute bacterial rhinosinusitis are the same as in AOM. *Streptococcus pneumonia* is the most prevalent.[13] Although antibiotics are more effective than placebo in the treatment of bacterial sinusitis, most cases (about 2/3) will resolve without antimicrobial therapy.[15] Serious complications are rare and most symptoms resolve without treatment. It is reasonable to use a 10 day course of watchful waiting prior to prescribing antibiotics for uncomplicated cases according to a recently released evidence report sponsored by the Agency for Health Care Policy and Research (AHCPR).[15] The report indicates the evidence does not justify the use of newer, more expensive antibiotics in uncomplicated, community-acquired, acute, bacterial rhinosinusitis, and recommends amoxicillin or TMP/SMX as antibiotics of choice.[15] Newer agents such as amoxicillin/clavulanate and cefuroxime axetil may play a role when the primary agents fail or in complicated cases. They have not demonstrated improved outcome over amoxicillin despite the increasing prevalence of beta-lactamase producing organisms.

Pharyngitis

Group A Streptococcal pharyngitis is the only common form of acute pharyngitis where antibiotic therapy is indicated.[16] The vast majority of acute pharyngitis cases seen in primary care are caused by viral infections. Group A Streptococcus accounts for only 15% of all cases.[17] According to two expert panel reports, the diagnosis of Group A Streptococcal pharyngitis should be confirmed by appropriate laboratory tests before initiating antibiotic therapy.[16,17] Signs and symptoms of Group A Streptococcus and viral pharyngitis overlap, and a positive diagnosis cannot be reliably made based on symptoms alone.[16,17] Clinical signs and symptoms may be more useful in determining when a diagnostic test is not needed. The presence of cough, rhinorrhea, hoarseness, conjunctivitis and diarrhea strongly suggest a viral etiology.[16]

Antimicrobial therapy has a number of proven benefits in the treatment of Group A Streptococcal pharyngitis, including prevention of acute rheumatic fever and suppurative complications like peritonsillar abscess.[16] Symptoms often resolve in as little as 3-4 days without treatment but penicillin therapy speeds recovery. It often produces dramatic improvement in as little as 24 hours, thus reducing infectivity and decreasing the spread of Group A Streptococcus.[16]

For patients with confirmed Group A Streptococcal pharyngitis, penicillin VK remains the treatment of choice.[16,17] Penicillin therapy for 10 days results in clinical and bacteriological cure in approximately 90% of patients.[17] Shorter courses of therapy have been less effective, and patients need to be counseled to complete therapy, even though symptoms may resolve after one or two days of treatment.[17] Penicillin VK can be administered twice or three times daily to improve compliance without compromising effectiveness.[16] Resistance of Group A Streptococcus to penicillin has not been reported. However, certain areas of Europe have experienced resistance to erythromycin.[17] In the United States, macrolide resistance is uncommon (less than 5%), and erythromycin is still a good choice for patients allergic to penicillin.[16]

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Intramuscular benzathine penicillin G may be preferred for patients unable or unlikely to complete the full course of oral treatment.[16] Amoxicillin and many oral cephalosporins are also effective, but have a broader spectrum and exert greater selective pressure for the development of antimicrobial resistance.[17] This also applies to the extended spectrum macrolides, clarithromycin and azithromycin.[17]

Acute Bronchitis

Acute bronchitis is a self-limiting condition in otherwise healthy individuals.[18] The most common cause is a viral pathogen.[18] An analysis of six placebo controlled trials of antimicrobial therapy in adults concluded that evidence does not support treatment of acute bronchitis with antibiotics.[19] Most studies show no, or at most, minimal improvement of symptoms. A CDC sponsored expert panel recommends that regardless of duration, a nonspecific cough illness/bronchitis in children rarely warrants antibiotic therapy.[18]

Despite the fact that most acute bronchitis episodes are viral in nature and resolve spontaneously, patients frequently receive antibiotics.[2,3] Generally, antibiotics are only indicated if a bacterial infection is confirmed. Pertussis should be treated according to established recommendations.[18] Occasionally, *Mycoplasma pneumoniae* can cause pneumonia and a prolonged cough illness and may warrant treatment with a macrolide or a tetracycline depending on the age of the patient.[18] However, the vast majority of prolonged cough illnesses are allergic, asthmatic, post-infectious or viral in nature, and do not respond to antibiotic treatment.[18] Of adults with uncomplicated rhinovirus infections, 20% continue to cough past two weeks after the onset of symptoms. The CDC expert panel recommends seeking a specific diagnosis in the initial management of a prolonged cough and avoid empiric antibiotic therapy.[18]

"A recent study indicated that patients were as satisfied or more satisfied with education than an antibiotic prescription for probable viral respiratory tract infections. Preservation of the doctor-patient relationship is not dependent on the patient walking out of the exam room with a prescription."

Patient Expectations and Education

Antibiotics are often prescribed at office visits for viral infections due to actual or perceived patient expectation for treatment. Parents' expectations of an antibiotic prescription, patient satisfaction and retaining customers for future visits were key factors in over prescribing by Atlanta pediatricians and family physicians in a CDC inquiry. A recent study indicated that patients were as satisfied or more satisfied with education than an antibiotic prescription for probable viral respiratory tract infections.[20] Preservation of the doctor-patient relationship is not dependent on the patient walking out of the exam room with a prescription.

It is important that the illness is not dismissed as "only a viral illness." Patients and/or parents should be provided education on the benefits and risks of treatment. It is important to emphasize that antibiotics increase the individual patient's risk of infection with drug-resistant organisms and plan treatment of symptoms. Prescribe analgesics, decongestants or other treatments where appropriate. A realistic time course for resolution of symptoms should also be discussed. To assist in the patient education process, the CDC has developed a variety of useful patient education handouts and tools for health care providers. These can be accessed and downloaded free of charge from the CDC's Internet site (http//www.cdc.gov/ncidod/ar/). An order form can also be completed at this web site to have copies of these materials mailed.

By adhering to the recommendations for judicious use of antibiotics for common respiratory tract infections developed by the CDC, the disturbing pattern of antimicrobial resistance that has occurred over the past decade may begin to reverse. ◘

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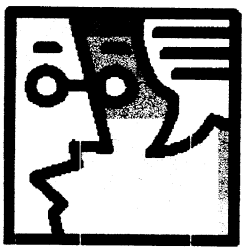
REFERENCES:

1. Dowell SF, Marcy SM, Phillips WR, et al. Principles of judicious use of antimicrobial agents for pediatric upper respiratory tract infections. Pediatrics 1998;101:163-5
2. Nyquist A, Gonzales R, Steiner JF, et al. Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis. JAMA 1998; 279(11):875-77
3. Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. JAMA 1997;278:901-4
4. Schwartz RH, Freij BJ, Ziai M, et al. Antimicrobial prescribing for acute purulent rhinitis in children: a survey of pediatricians and family practitioners. Pediatr Infect Dis J 1997;16:185-90
5. Dowell SF, Marcy SM, Phillips WR, et al. Otitis media-principles of judicious use of antimicrobial agents. Pediatrics Supp 1998;101:165-71
6. Froom J, Culpepper L, Jacobs L, et al. Antimicrobials for acute otitis media? A review from the International Primary Care Network. BJM 1997; 315:98-102.
7. Rosenfeld RM, Vertrees JE, Carr J, et al. Clinical efficacy of antimicrobial drugs for acute otitis media: meta-analysis of 5400 children from thirty-three randomized trials. J Pediatrics 1994;124:355-67
8. Conrad DA. Should acute otitis media ever be treated with antibiotics? Pediatric Annals 1998;27(2):66-74
9. Dowell SF, Butler JC, Giebink GS, et al. Acute otitis media: management and surveillance in an era of pneumococcal resistance-a report from the Drug-resistant streptococcus pneumoniae Therapeutic Working Group. Pediatr Infect Dis J 1999;18:1-9
10. Kozyrskyj AL, Hildes-Ripstein GE, Longstaffe SEA, et al. Treatment of acute otitis media with a shortened course of antibiotics: A meta-analysis. JAMA 1998; 279(21):1736-42.
11. Paradise JL. Short course antimicrobial treatment for acute otitis media: Not best for infants and young children. JAMA 1997; 278(20):1640-42
12. Adderson EE. Preventing otitis media: Medical Approaches. Pediatric Annals 1998; 27(2):101-07
13. O'Brien KL, Dowell SF, Schwartz B. Acute sinusitis-principles of judicious use of antimicrobial agents. Pediatrics Supp 1998; 101:174-77
14. Fagnan LJ. Acute sinusitis:a cost-effective approach to diagnosis and treatment. Am Fam Phys 1998;58:1795-1802
15. Diagnosis and treatment of acute bacterial rhinosinusitis. Summary, evidence report/technology assessment: #9, March 1999. Agency for Health Care Policy and Research, Rockville, MD. http://www.ahcpr.gov/clinic/sinussum.htm
16. Bisno AL, Gerber MA, Gwaltney JM, et al. Diagnosis and management of group A streptococcal pharyngitis: A practice guideline. Clinical Infectious Diseases 1997; 25:574-83
17. Schwartz B, Marcy SM, Phillips WR, et al. Pharyngitis-principles of judicious use of antimicrobial agents. Pediatrics 1998;101:171-4
18. O'Brien KL, Dowell SF, Schwartz B, et al. Cough illness/bronchitis - principles of judicious use of antimicrobial agents. Pediatrics 1998;101:178-81
19. Orr PH, Scherer K, Macdonald A, et al. Randomized placebo-controlled trials of antibiotics for acute bronchitis: a critical review of the literature. J Fam Pract 1993;36:507-12
20. Hamm RM, Hicks RJ, Bemben DA. Antibiotics and respiratory infections: are patients more satisfied when expectations are met? J Fam Pract 1996;43:56-62

■ **GASTROINTESTINAL** continued from page 3

REFERENCES:

1. Agreus L and Talley N. Challenges in managing dyspepsia in general practice. BMJ 1997;315:1284-1288
2. American Gastroenterological Association. American Gastroenterological Association Medical Position Statement: Evaluation of Dyspepsia, Gastroenterology 1998;114:579-581
3. British Society of Gastroenterology. Dyspepsia Management Guidelines. London:BSG, 1996
4. American Digestive Health Foundation. Report of the International update conference on Helicobacter pylori 1997 www://gastro.org/hpupdate.html 2/2/99
5. Blaser MJ, Science, medicine and the future:Helicobacter pylori and gastric diseases. BMJ 1998;316:1507-1510
6. Veldhuyzen van Zanten SJO et al. Helicobacter pylori:new developments and treatments. CMAJ 1997;156(11):1565-1574
7. Soll AH. Medical treatment of peptic ulcer disease; Practice Guidelines. JAMA 1996;275:622-629
8. Talley NJ and Hunt RH. What role does Helicobacter pylori play in dyspepsia and non-ulcer dyspepsia? Arguments for and against H pylori being associated with dyspeptic symptoms. Gastroenterology 1997;113:s67-s77
9. Canadian Helicobacter pylori Consensus Conference. Can J Gastroenterol 1998 12(1)31-41
10. Friedman LS. Helicobacter pylori and nonulcer dyspepsia. New Eng JMed 1998;339:1928-1930
11. Scott M and Gelhot AR. Gastroesophageal reflux disease: Diagnosis and management. Am Fam Physician 1999;59(1):1161-1169
12. Galmiche JP et al. Treatment of gastro-oesophageal reflux disease in adults. BMJ 1998;316:1720-1723
13. Reynolds JC. Influence of pathophysiology, severity and cost on the medical management of gastroesophageal reflux disease. Am J Health-Syst Pharm 1996;53(suppl 3):s5-12
14. Horn JR. Use of prokinetic agents in special populations. Am J Health-Syst Pharm 1996;53(suppl 3):s27-29
15. Chiba N et al. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: A meta-analysis. Gastroenterology 1997;112:1798-1810
16. Bardham KD et al. Symptomatic gastro-oesophageal reflux disease; double blind controlled study of intermittent treatment with omeprazole or ranitidine. BMJ 1999;318:502-7
17. Harris RA et al. Prevention of Recurrences of erosive reflux esophagitis: A cost effectiveness analysis of maintenance proton pump inhibition. Am J Med 1997; 102: 77-78
18. Bateman DN. Proton pump inhibitors: three of a kind? Lancet 1997; 349: 265-269
19. Prakash A and Faulds D. Rabeprazole. Drugs1998;55(2):261-267
20. Feret B et al. Rabeprazole: A proton pump inhibitor for the treatment of acid related disorders. Formulary 1999;34:313-323
21. Fitton A and Wiseman L. Pantoprazole. A review of its pharmacological properties and therapeutic use in acid related disorders. Drugs 1996;51(3)460-482



Antipsychotic Medication Doses: A Reader Responds

To The Editor: The July 1999 DUR Newsletter[1] contained information that conflicts with clinical experience of psychiatrists working in community mental health centers with the chronically mentally ill population.

Figure 3, Page 5 states no increased benefits above 6 mg/d of risperidone and 20 mg/d of olanzapine. I follow several hundred patients and have used these medications since they were first released. Certain patients require 16 to 18 mg/d of risperidone and experience significant psychosis at less than 30-40 mg of olanzapine per day. Of course, this is not a majority of patients, but is a significant minority, especially with olanzapine. These doses do increase side effects and change the side effect profiles.

I've been highly motivated to use lower doses. But even with very gradual decreases and careful monitoring, some patients become psychotic and get into trouble. Unfortunately, I've sent several patients to a hospital inpatient admission (a few have ended up in jail) in the process of very slowly decreasing the doses of those medications. The other option is to add a little of a typical neuroleptic and that's sometimes necessary in a certain sub-sample.

Alan Cohn, MD
Lane County Mental Health, Eugene, OR

Dr. Wilson replies: *I couldn't agree with you more. The statements in the newsletter should have noted that the doses above 6 mg/d of risperidone or 20 mg/d of olanzapine "are of no benefit* ***to most patients****."*

For the majority of patients, doses of risperidone above 6 mg/d are less effective and lead to more motor system side effects than do lower doses.[2] The large clinical trials of olanzapine did not study the effectiveness of doses above 20 mg/d. However, the toxicity of this agent increases as the dose is raised above 20 mg/d, and the pharmacy costs become extremely high.

Even with the new antipsychotics, at the optimal doses, many patients do not respond adequately. In a typical clinical trial, at the most effective dose, two-thirds of the patients will be rated as somewhat or much improved. That leaves a third of the patients with a less than satisfactory response. Remarkably little controlled research addresses the issue of treating non-responders, or of optimizing response in the "somewhat better" patients. A recent controlled study of haloperidol demonstrated that both dose increases and decreases benefit some otherwise non-responsive patients.[3] In the pre-clozapine days, we wrote detailed algorithms for treating the non-responding patients.[4] Despite the clear success of the newer agents, sub-optimal response is a clinical reality. A wealth of uncontrolled evidence (such as your personal experience, and my own) suggests that some of these treatment refractory cases will benefit from non-standard dosing or combinations of medications. Credible case reports note response to higher doses of olanzapine.[5] Keeping up with current clinical practice is not easy. However, respected newsletters[6,7] report up-to-the-minute thought within the psychopharmacologic community. Moderated professional forums on the Internet are increasingly taking the place of brief communications in the literature. An archive of one of these forums is available to the general public.[8]

So what should we do? First off, primary care physicians would do well to practice within the well established dose guidelines and to avoid unusual combinations. Generalists should obtain psychiatric consultation when their patients do not respond to treatment. Psychiatrists should use standard, simple treatments as the first line for all patients. However, when the well studied approaches do not result in an acceptable treatment outcome, less studied, but clinically reasonable, approaches may be considered. Informed consent should be obtained. Treatment should be monitored closely and the novel approaches discontinued if there is no clear benefit. Pharmacists, administrators and regulators have the daunting task of developing ways to distinguish the careful, responsible treatment of individuals with refractory problems from indiscriminate use of untested, non-standard treatments.

If we do these things, each patient will achieve the best possible outcome from treatment with our increasingly powerful, but still imperfect, psychopharmacology.

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REFERENCES:

1. Wilson WH, Varley H. Atypical antipsychotic agents in the treatment of schizophrenia, Oregon DUR Newsletter 2:1 (July), 1999
2. Pies R. Individualized risperidone dosing. Am J Psychiatry 156(7):1123-1124, 1999.
3. Coryell W, Miller DD, Perry PJ. Haloperidol plasma levels and dose optimization. Am J Psychiatry 155(1):48-53, 1998
4. Simpson GM, Wilson WH. Strategies for treating non-responding schizophrenics, in Schizophrenia, Scientific Progress, SC Schulz & Carol Tamminga (eds). New York: Oxford University Press, 1989
5. Reich J. Use of high-dose olanzapine in refractory psychosis (letter). Am J Psychiatry 156(4):661, 1999
6. Biological Therapies in Psychiatry Newsletter. Gelenberg AJ (ed). Gelenberg Consulting and Publishing, Tucson, AZ
7. Currents in Affective Disorders. Rosenblatt JE and Rosenblatt NC (eds)Currents Publications Ltd, Bethesda, MD
8. Psychopharmacology Tips web page. Hsiung R (webmaster) http://uhs.bsd.uchicago.edu/~bhsiung/tips/tips.html

We hope you found this issue of the Oregon Drug Use Review Board Newsletter useful as well as thought-provoking and interesting. We welcome your questions, concerns, comments or ideas regarding the newsletter. Address correspondence to the managing editor:

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