Drug Monitor

Antibiotics in the ED

Although inappropriate antibiotic prescribing for acute respiratory tract infection (ARTI) has declined in recent years, it's still a problem, say researchers from the University of North Carolina School of Pharmacy, Chapel Hill. Using a national database, they identified more than 50 million emergency department (ED) visits for ARTIs between 1995 and 2000—62% of which resulted in an antibiotic prescription. In the subset of ARTIs (such as nasopharyngitis and acute bronchitis) for which antibiotic therapy is nearly always inappropriate, antibiotic prescriptions decreased significantly over the six-year period, from 57% to 45%.

When children's visits were considered separately, the downward trend was seen almost exclusively in urban hospitals; prescribing patterns remained virtually unchanged in more rural areas. Furthermore, children with ARTIs were more likely to be prescribed an antibiotic in the ED if they presented after 10 PM and if the provider was a staff physician or prescribing nonphysician, rather than a resident or intern physician. In adults, time of day, provider type, and hospital location appeared to have little effect on antibiotic prescribing.

Acknowledging the limitations of a population-based study in which there was little clinical information about the patients and no way to verify the ARTI diagnoses, the researchers nevertheless feel their results "suggest an important role for pharmacists in promoting appropriate antibiotic use." They contend that both community pharmacists (as a first contact for many patients with upper respiratory infections and their caregivers) and hospital-based pharmacists (as consultants for ED providers in drug selection) have opportunities to intervene before inappropriate prescriptions are made. In addition, the researchers call for drug utilization reviews that are tailored to the unique situations found in emergency medicine and, specifically, in rural EDs.

Source: *Ann Pharmacother.* 2004;38:928–935.

Diabetic Neuropathy: Patch It Up

For patients with painful diabetic polyneuropathy (DPN), treatment often is inadequate and limited by systemic effects. But researchers from the University of Rochester School of Medicine and Dentistry, Rochester, NY and Southern Drug Research, Birmingham, AL found the 5% lidocaine patch could improve pain and quality-of-life outcomes significantly, with minimal adverse events and no systemic drug accumulation.

The 56 patients in this open-label study had clinically defined painful DPN that had persisted for at least three months. For three weeks, patients applied up to four patches daily to the area of worst pain for 18 hours at a time. No new analgesics or increased doses of prior analgesics were allowed. At one of the three study sites, lidocaine patch treatment was extended another five weeks, during which concomitant analgesic therapy was tapered while maintaining adequate pain control.

After three weeks, 37 (70%) of the 53 patients who completed treatment reported pain scores that were at least 30% lower than baseline. This included both patients with and those without allodynia (68% and 71% of these patients, respectively). Furthermore, six (32%) of the patients with allodynia and 17 (50%) of those without allodynia reported pain scores that reflected a greater than 50% improvement.

Sleep quality and other aspects of pain-influenced quality of life also improved. Among the 28 patients who received an additional five weeks of patch treatment, seven tapered their concomitant pain medications—with three discontinuing them completely and four maintaining a reduced dosage.

Source: *Arch Neurol.* 2004; 61:914–918.

Targeting B Cells in RA Treatment

The exact pathogenesis of rheumatoid arthritis (RA) remains a medical mystery, but there's accumulating evidence that B cells play a

key role in the process. After an open-label study in which patients with RA responded well to rituximab, a medication currently indicated for refractory CD20 B cell non-Hodgkin's lymphoma, researchers conducted an international, multicenter, randomized, double-blind, controlled study. They found that, for patients whose RA had remained active despite methotrexate treatment, a single course of two rituximab infusions significantly improved RA symptoms at 24 and 48 weeks.

The researchers randomly assigned 161 patients to one of four treatments: oral methotrexate plus two placebos (the control group), IV rituximab plus two placebos, IV rituximab plus IV cyclophosphamide and one oral placebo, or IV rituximab plus oral methotrexate and one IV placebo. All groups received concomitant corticosteroids as well as oral leucovorin calcium (folinic acid) therapy to counter methotrexate's adverse effects.

Rituximab treatment was associated with nearly complete depletion of peripheral blood B cells and a rapid decrease in rheumatoid factor levels that was "pronounced" and maintained at week 24. This corresponded to a significantly higher proportion of patients who achieved a 50% reduction in RA symptoms with rituximab plus either methotrexate or cyclophosphamide than with methotrexate alone. In all three rituximab groups, the proportion of patients who achieved a 20% symptom reduction was higher than it was in the control group. In the rituximab-methotrexate group, improvements were sustained at 48-week follow-up.

The incidence of adverse events was similar across all four groups, and the majority of events associated with rituximab were mild to moderate. Of five patients who had serious infections, however, four were receiving rituximab. Immunoglobulin levels appeared to be only minimally affected by rituximab treatment, and antitetanus antibody titers (a measure of previously acquired immunity) were unaffected.

Source: *N Engl J Med*. 2004; 350:2572–2581.

Doxycycline for Urethral Syndrome

When the cause of persistent urinary urgency and frequency and chronic urethral or pelvic pain—sometimes known as urethral syndrome—is elusive and various antibiotic regimens provide only transient relief, women with these symptoms often are diagnosed with interstitial cystitis (which implies chronic, progressive, and often untreatable disease) or even referred to a psychiatrist. Before taking these steps, though, researchers from the University of Berne, Switzerland suggest trying doxycycline.

In these patients, the researchers say, cystoscopy often reveals hyperemia, increased vascularization of the urethra, pseudopapillary papillomas at the bladder neck, and trigonal leukoplakia (a whitish opaque membrane extending from the bladder neck along the trigone). They consider these findings to be signs of chronic infection, though they add that literature supporting this hypothesis is rare. They theorized that women presenting with urinary symptoms of unknown origin and trigonal leukoplakia, but without conventional urinary tract infection, might benefit from treatment with the broad spectrum antibiotic doxycycline and a vaginal bactericide or antimycotic.

A total of 103 women who had a long history of painful urinary symptoms despite short-term antibiotic therapy were treated with doxycycline 100 mg twice daily for two weeks, followed by 100 mg once daily for another two weeks. In addition, they were given vaginal tablets of hexetidine or ciclopirox olamine once daily for 10 days. To prevent possible reinfection through sexual transmission, the researchers also treated the patients' sexual partners with doxycycline 100 mg twice daily for two weeks and advised them to use condoms for the four-week study period.

At follow-up (median, three months; range one to 70 months), 73 (71%) of the women considered themselves either cured or improved, 29 (28%) reported no change, and one (1%) described her symptoms as worse. Among the 31 patients who consented to follow-up cystoscopy (16 who felt cured or improved, 14 who felt unchanged, and the one who felt worse), eight showed complete resolution of trigonal leukoplakia and 12 showed a reduction in the degree of leukoplakia.

Although they were able to identify an infecting organism in only 15% of their patients, the researchers explain that many proposed organisms aren't recognized by standard microbiological assays. They say their findings should encourage a thorough prospective microbiological search using the most advanced diagnostic tools available in patients with apparent refractory, chronic irritative bladder symptoms.

Source: *J Urology*. 2004; 172:232–235.

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Switching Thiazolidinediones

When troglitazone was removed from the market in March 2000, VA patients nationwide who'd been taking the drug needed to be switched to rosiglitazone or pioglitazone. But because the potency, dosing equivalents, and safety of those drugs hadn't been assessed specifically in VA patients, the VA's Pharmacy Benefits Management Strategic Healthcare Group performed a national drug utilization evaluation at nine VA sites.

Each site was provided with the recommended conversion doses. After a one-week washout period, patients who'd been taking troglitazone 200 to 400 mg were advised to switch to rosiglitazone 4 mg or pioglitazone 15 mg, and those who'd been taking troglitazone 600 mg were advised to switch to rosiglitazone 8 mg or pioglitazone 30 mg. Patients were assessed monthly for four months.

Of the 362 patients switched at the nine sites between November 1999 and October 2000, 101 (28%) were converted to pioglitazone and 261 (72%) to rosiglitazone. Most patients (250, or 69%) began with the recommended conversion dose, but 40 (11%) started at a higher dose and 72 (20%) started at a lower dose. Of those who started low, 46% required an upward adjustment in their dose, compared with 29% of those who started at the recommended dose. Only two patients had their dose decreased—a number too small to analyze.

Overall, 28% of the patients switched to pioglitazone and 16% of those switched to rosiglitazone needed a dose increase. This suggests the subpotency of the recommended conversion doses, the researchers say. Rather than recommending a higher starting dose, however, they advise monitoring patients—especially those converted to pioglitazone—closely in case a dose increase is needed.

While the researchers found no "significantly alarming results" with regard to adverse drug effects, they say the frequency of such effects (in particular, those relating to new-onset or exacerbated congestive heart failure) warrant detailed monitoring of all patients given a thiazolidinedione. On the basis of this recommendation, the VA has established a national thiazolidinedione registry.

Source: *Formulary*. 2004; 39:310–317.

Phase III Trial of Heart Failure Drug Halted

"Compelling" benefits led NitroMed (Lexington, MA) to stop a phase III trial of its combination drug isosorbide dinitrate-hydralazine a year ahead of schedule in order to give placebo patients an opportunity to take it as well. Preliminary data indicate that the drug, when used as an adjunct to other cardiovascular medications (including beta-blockers, angiotensin antagonists, aldosterone inhibitors, digoxin, and diuretics), significantly improves survival and reduces adverse events in black patients with heart failure.

In the United States, blacks are disproportionately affected by heart failure and other cardiovascular diseases—with higher rates of mortality. Though socioeconomic factors and inadequate access to medical care have been proposed as reasons for this disparity, there's evidence that certain medications currently used for heart failure are less effective in the black population.

Isosorbide dinitrate is a nitric oxide donor, and hydralazine is an antioxidant and vasodilator. Used alone, neither is indicated for heart failure. But researchers believe the combined action of the two substances may alleviate the nitric oxide deficiency that some consider particularly important in heart failure in the black population.

The double-blind, randomized, placebo-controlled African American Heart Failure Trial (A-HeFT) enrolled more than 1,000 patients from 170 sites across the United States, making it the largest database of black patients with heart failure to date, according to the Association of Black Cardiologists, a cosponsor of the trial. NitroMed plans to work closely with the FDA to complete the necessary data analysis—and hopes to be ready to launch the new drug in early 2005. ●

Sources: PharmaLive News Release. July 19, 2004.

NitroMed BiDil web site. Available at: www.nitromed.com/BiDil.shtml. Accessed July 19, 2004.

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