

Consider Nitrofurantoin in Bacterial-Resistance Era

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WASHINGTON — Nitrofurantoin should be considered as a fluoroquinolone-sparing agent for women with mild to moderate symptoms of uncomplicated cystitis, Dr. Thomas M. Hooton said at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

Nitrofurantoin, first approved in 1953 for the treatment of urinary tract infection (UTI), has been overshadowed in the last several decades, first by trimethoprim-sulfamethoxazole (TMP-SMX), and more recently by fluoroquinolones. But the old drug's role is being reexamined in light of increasing antimicrobial resistance. "Nitrofurantoin is over 50 and still going strong," said Dr. Hooton, professor of medicine at the University of Washington, Seattle.

Guidelines issued in 1999 by the Infectious Diseases Society of America listed TMP-SMX as first-line treatment for uncomplicated, acute, symptomatic bacterial cystitis except when resistance is greater than 10%-20%, in which case fluoroquinolones should be used (Clin. Infect. Dis. 1999;29:745-58).

Nitrofurantoin, the IDSA said at the

time, "may become more useful as resistance to TMP-SMX increases," but was not considered first-line because of concerns about effectiveness (85% cure rate versus 90%-95% for other first-line agents) and safety, particularly regarding the rare but potentially serious occurrence of acute pulmonary reaction and the even rarer peripheral neuritis.

Although it's important to keep those concerns in mind, several new developments have occurred since those guidelines were issued that may shift the risk/benefit calculation, Dr. Hooton said.

One is the dramatic rise in resistance of *Escherichia coli* causing uncomplicated cystitis in women. In a Seattle study conducted over a 5-year period during the 1990s, *E. coli* resistance to TMP-SMX doubled, from 9% to 18%, whereas resistance to nitrofurantoin and ciprofloxacin remained unchanged, at 0%-2% for the entire study period (JAMA 1999;281:736-8).

Moreover, a safety review of published and unpublished data on nitrofurantoin re-

vealed an extremely low rate (0.00094%) of acute pulmonary reactions and even lower rates of other major adverse events (Drugs 2001;61:353-64).

Most reported adverse events occurred in patients using nitrofurantoin for long-term UTI prophylaxis and few studies have

evaluated either efficacy or safety of short-term nitrofurantoin use. With that in mind, Dr. Hooton and his associates recently completed a randomized trial aimed at demonstrating noninferiority (difference of 10%

or less) of 5-day nitrofurantoin (Macrobid) 100 mg twice daily, compared with TMP-SMX 160/800 mg twice daily in 303 healthy nonpregnant women aged 18-45 years with uncomplicated acute cystitis.

As expected, the majority (86%) of infections were due to *E. coli*, 8% were due to *Staphylococcus saprophyticus*, and another 2% to group B streptococcus. Resistance to TMP-SMX was 12%, compared with 3% to nitrofurantoin. Clinical cure rates were approximately 90% at 5-9 days

and 80% at 28-30 days for both treatment groups. Microbiologic cure rates are still being evaluated, Dr. Hooton said.

The proportion of women who reported having taken all doses was 95% for the 5 days of nitrofurantoin and 99% for the 3-day TMP-SMX regimen. There were no significant differences in adverse events, reported by approximately 40% in both treatment groups. Gastrointestinal side effects were the most common in both groups. The proportion of subjects who discontinued because of side effects was 1% for TMP-SMX and 2% for nitrofurantoin, whereas 11% of the TMP-SMX group required treatment for an adverse event, compared with 6% for nitrofurantoin, he said.

Considering all these recent data—and the fact that nitrofurantoin and TMP-SMX are available in generic formulation, whereas none of the fluoroquinolones except ciprofloxacin are—it might make sense to reserve fluoroquinolones for women who are allergic to TMP-SMX or have risk factors for resistance, have moderate to severe symptoms clearly affecting their daily routine, or who might find it difficult to return for care, Dr. Hooton said at the conference, sponsored by the American Society for Microbiology. ■

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