Nitrofurantoin (MACROBID) vs Trimethoprim/Sulfamethoxazole in Women with Acute Uncomplicated Cystitis[1]

BOTTOM LINE

- In this study, women with acute uncomplicated cystitis were randomized to open-label treatment with either trimethoprim/sulfamethoxazole **(TMP/SMX) for 3 days** or **nitrofurantoin for 5 days**.
- Nitrofurantoin was equally efficacious to TMP/SMX and had a similar rate of adverse effects.
- **Five days of nitrofurantoin is an effective and safe first-line option in this patient population.**[2 IDSA 2010 (IA)]
- Also of note, three days of TMP/SMX had a similar clinical cure rate even though pathogens were less susceptible. Of interest, TMP/SMX worked ~50% of the time even in those where culture results suggested non-susceptible.

BACKGROUND

- At the time of this study, nitrofurantoin was a 1st line agent for UTIs. However, it was unclear if a 5 day course was appropriate, and 7 day courses were commonly used.[3,4] This study compared 5 days of nitrofurantoin to 3 days of TMP/SMX.[1]

TRIAL BACKGROUND

DESIGN: computer randomized, open-label, controlled, equivalence trial. Enrollment period: January 2002 – December 2005. Funding: Procter & Gamble Inc (MACROBID manufacturer) and US Public Health Service. Setting: outpatient clinic in Seattle.

INTERVENTION: Nitrofurantoin (MACROBID) 100mg PO BID for 5 days vs TMP/SMX 1 DS tablet PO BID for 3 days. Follow up: clinical cure assessed on day 3 of therapy; follow-up visits 5 to 9 days & 28 to 30 days after therapy completion.

INCLUSION:

Women age 18-45 years of age who were in good general health, and who had symptoms of acute cystitis (dysuria, frequency, and/or urgency) and a urine culture with at least 10^2 CFU/mL of a uropathogen.

EXCLUSION:

Pregnancy, lactating, not using regular contraception, diabetes, known anatomical abnormalities of the urinary tract, recent (< 2 weeks) exposure to an oral or parenteral antimicrobial agent, or who were currently using prophylactic antibiotic drugs.

POPULATION randomized: n=338; case-based analysis: n=308

- Median age 21 (18-41), 84% never married, 73% white, 25% ≥3 lifetime UTIs, 95% sexually active in past month, 22% spermicide use in past month.
- ***E. coli*** was the detected pathogen in 82% of isolates (99.6% were susceptible to nitrofurantoin, 88% were susceptible to TMP/SMX). Other detected pathogens included *Staphylococcus saprophyticus*, *Enterococci*, *Klebsiella*, *Proteus mirabilis*, *Enterobacter*, and Group B *Streptococci* (of these non-*E. coli* pathogens, 90% were susceptible to nitrofurantoin and 77% were susceptible to TMP/SMX). In total, 3 patients in the nitrofurantoin group grew a pathogen not susceptible to nitrofurantoin, and 17 patients in the TMP/SMX group grew a pathogen not susceptible to TMP/SMX.

RESULTS

follow-up: 30 days

TABLE 1: EFFICACY

CLINICAL ENDPOINTS	NITROFURANTOIN 100 MG BID X 5 DAYS n=160	TMP/SMX 1 DS TABLET BID X 3 DAYS n=148	ARR (95% CI)	COMMENTS
PRIMARY ENDPOINT				• While TMP/SMX had poorer susceptibility results than nitrofurantoin, there was still no significant difference in cure rates. • Majority of failures were due to cystitis symptoms; 1.4% (n=2/148) developed pyelonephritis in the TMP/SMX group. • Within the TMP/SMX group, clinical cure was achieved in 84% (n=110/130) of TMP/SMX susceptible-uropathogens, & in 41% (n=7/17) of TMP/SMX non-susceptible uropathogens (NHH=3, p<0.001). • Within the nitrofurantoin group, clinical cure was achieved in 67% (n=2/3) of nitrofurantoin non-susceptible uropathogens.
Clinical cure after 30 days after therapy completion*	84%	79%	-5 (-13 to 4) *not significant*	
SECONARY ENDPOINTS				
Early microbiological cure rates 5-9 days after therapy completion	92%	91%	-1 (-7 to 6) *not significant*	
Early clinical cure rates 5-9 days after therapy completion	90%	90%	-0.1 (-7 to 7) *not significant*	

*A clinical cure was defined as women who DID NOT require antimicrobial drug treatment for lack of resolution of initial UTI symptoms or for new UTI symptoms. These symptoms were assessed using a questionnaire on follow-up visits at both 5-9 days and 28-30 days.

TABLE 2: SAFETY

ADVERSE EFFECTS	NITROFURANTOIN 100 MG BID X 5 DAYS n=160	TMP/SMX 1 DS TABLET BID X 3 DAYS n=148	COMMENTS
Reported an adverse effect as assessed by an open ended question	28%	31%	• The most common adverse effects were nausea, diarrhea, headache, light-headedness or vaginal itching. The study did not expand on the occurrence of specific adverse effects in each group. • When adverse effects required treatment, most often over-the-counter medications were used.
Reported at least one adverse effect when assessed by direct questioning	39%	41%	
Adverse effect leading to discontinuation	2%	1%	
Adverse effect requiring treatment	6%	11%	

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Well designed study: adequate sample size, minimal differences in baseline characteristics between groups, allocation concealment used.
- Outpatient study setting generalizable to majority of acute uncomplicated patients.
- Evaluated outcomes stratified by susceptibility of the infecting uropathogen (therefore able to see if any treatment differences explained by resistance).
- Studied an important clinical question.

LIMITATIONS:

- Study was open-label and primary outcome (i.e., clinical cure) as well as adverse effects was subjective; however, microbiological cure was objective and consistent with primary outcome findings.
- Study utilized a case-available analysis which did not include the patients lost to follow up, etc (n=11 in nitrofurantoin group, n=19 in TMP/SMX group) in final analysis. However, results consistent with intention to treat analysis.
- Unknown whether rare, more severe adverse effects were assessed; however, study was likely too small to capture these adverse effects.
- The occurrence of each specific adverse effect was not listed, rather just a total percent of adverse effects per group.
- Only women only in the nitrofurantoin group collected midstream urine after three days of therapy.
- Reporting bias was present as methods report that clinical cure was assessed at three days of therapy; however, only microbiology cure was reported.
- Highly compliant (≥97%), white, student population. Are the results generalizable?

UNCERTAINITIES:

- Is the 5-day nitrofurantoin regimen similar to TMP/SMX in areas with higher nitrofurantoin resistance?
- Women with cystitis symptoms and ≥ 10^2 CFU/mL of a uropathogen were included in the study; however, some references consider cystitis in those with symptoms and ≥ 10^5 CFU/mL of a uropathogen.[5]
- Although the study was not designed to specifically evaluate a 3-day regimen of nitrofurantoin, it does demonstrate that most women (98%) had microbiological cure by 3 days of therapy. This is in contrast to a study performed previously in a similar population where only 82% had microbiological cure by 3 days of therapy.[6]

COST: Nitrofurantoin (MACROBID) $19/5days.
Trimethoprim/sulfamethoxazole (BACTRIM, SEPTRA, Cotrimoxazole), g $11/3 days.

RxFILES RELATED LINKS

- RxFiles UTI Treatment Chart: http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-UTI-Tx.pdf
- RxFiles ABX-2 Newsletter: http://www.rxfiles.ca/rxfiles/uploads/documents/ABX-2-Newsletter-Cystitis-and-SSTI.pdf

BID=twice daily **CFU**=colony forming unit **CI**=confidence interval **DS**=double strength (1DS tab= 160/800mg) ***E coli*=*Escherichia coli*** **n**=number **NNH**= number needed to harm **TMP/SMX**=trimethoprim/sulfamethoxazole **UTI**=urinary tract infection

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References:

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6) Hooton TM , Winter C , Tiu F et al . Randomized comparative trial and cost analysis of 3-day antimicrobial regimens for treatment of acute cystitis in women. JAMA 1995; 273: 41–5.