What is the risk of pulmonary toxicity with nitrofurantoin (MACROBID)?

BOTTOMLINE

- **Nitrofurantoin-associated pulmonary toxicity** is rare & has been reported in both cystitis tx and prophylaxis settings. Majority of cases are reported in patients receiving therapy for longer than 5 days (recommended duration for cystitis tx[IDSA]).
- **Pharmacovigilance and health records data**: In patients taking one or more nitrofurantoin prescription(s) the risk of an **acute pulmonary reaction is 1 in 5000** nitrofurantoin users and of a **chronic pulmonary reaction (e.g., pulmonary fibrosis) is 1 in 750 to 7,500** nitrofurantoin users. Risk appears greater as age increases.
- **If prescribing nitrofurantoin for acute cystitis treatment:** Instruct patient to report fever, change in breathing, more shortness of breath or cough.
- Nitrofurantoin is **not recommended** as 1st line treatment for recurrent cystitis prophylaxis due to the risk of adverse events, including pulmonary reactions, which can lead to permanent impairment in chronic users (see also: RxFiles Risk of Peripheral Neuropathy with Nitrofurantoin Q&A). **If prescribing nitrofurantoin for recurrent cystitis prophylaxis:** Instruct patient to report change in breathing, more shortness of breath or cough and consider baseline and every 6 mons CXR and/or PFT. Reassess nitrofurantoin's indication at **6**-12 mos. Stop nitrofurantoin if the pt develops a UTI while on prophylaxis.
- **If you suspect pulmonary toxicity**: Discontinue nitrofurantoin; if severe reaction (hypoxia, respiratory symptoms) or no improvement 24-72 h after withdrawal consider corticosteroids; if bronchospasm present consider bronchodilators.

BACKGROUND[1-18]

- While there is extensive clinical experience with nitrofurantoin, its overall safety profile is somewhat unclear, as it was was approved by the FDA in 1953 prior to robust drug development requirements. Safety data is largely observational with limitations of confounding & selection bias.
- Nitrofurantoin's monograph includes a serious warning regarding the potential risk of pulmonary reactions. These pulmonary reactions are typically stratified into the following groups, each with varying characteristics:[1-15]

Characteristics	Acute/Subacute Reaction*	Chronic Reaction
Timeframe	***Acute***: ≤ 1 month; rapid onset, within hrs (if previously sensitized) or wks. ***Subacute****:* onset 1 to 6 months	≥6 months to years Insidious onset (average 30 months)
% of reactions	80-90%	10-20%
Pathophysiology	Immunologic/hypersensitivity (? non-dose related)	Toxic (e.g., O_2 radicals)(? dose related)
Clinical Presentation	**Fever** (occurs less often in *subacute rxns*), chills, malaise Chest pain/discomfort Tachypnea, dyspnea, cough (typically nonproductive), crackles or rales Myalgia/arthralgia, rash, pruritus	Fever (rare), malaise, fatigue Tachypnea, **progressive dyspnea, persistent cough** (typically nonproductive), altered pulmonary function
Labs	**Eosinophilia** (occurs less often and is less deranged in *subacute rxns)*; May also ↑WBC, neutrophils, ESR	Eosinophilia (occurs less often and is less deranged than acute rxns)
CXR	Pulmonary opacities ± pleural effusion; -typically bilateral and affecting lower lobes -10% normal CXR	Diffuse interstitial pneumonitis and/or fibrosis -pleural effusion (<10%)
Chest CT	Bilateral ground glass opacities	Mixed (ground glass opacities, consolidations, fibrosis)
Prognosis	**Reversible** -sx resolve within 1 week (50% within 24 hours, 90% within 72 hours) in acute rxns & within wks to months in *subacute rxns* after nitrofurantoin discontinuation -eosinophilia & CXR may take longer to resolve **Mortality: 0.5%** (~ ≤ 1/1,000,000 prescriptions)	**Permanent, sometimes reversible** -sx may resolve within months to years if recognized early after sx onset; however, pulmonary impairment (dyspnea or cough) may be permanent even after nitrofurantoin discontinuation **Mortality: 8%**

* *Subacute reactions* have not been as well studied, and thus there is less information describing the reaction.

- Nitrofurantoin is recommended 1st line for treatment of acute uncomplicated cystitis (nitrofurantoin 50 mg PO QID or MACROBID 100 mg PO BID x 5 days).[IDSA 2010 (A-I, strong recommendation based on high quality evidence)]
  - Uncomplicated cystitis is typically defined as cystitis in premenopausal, non-pregnant ♀ with no known urological abnormalities or comorbidities.[16]
- In recurrent cystitis (≥2 UTIs in 6 months or ≥3 UTIs in 12 months), reserve nitrofurantoin prophylaxis due to risk of AEs.
  - The Beers Criteria for potentially inappropriate medication use recommends avoiding long-term nitrofurantoin for cystitis prophylaxis in patients ≥ 65 yrs due to potentially irreversible pulmonary fibrosis concerns. [AGS 2015 (strong recommendation, low quality of evidence)]
  - TMP/SMX or TMP are 1st line tx options for recurrent cystitis (other options include cephalexin, FQs, or fosfomycin).

LITERATURE REVIEW[10-12,19-25]

Cystitis Treatment

Hutter et al. 2015:[19] meta-analysis of controlled trials (N=27 trials [N=24 RCTs], n=4807) assessing lower UTI treatment
- nitrofurantoin (≤ 14 days) for vs. active comparator/placebo: no pulmonary toxicity events

Comments: majority of trials were conducted 1970-90s & poor quality (Cochrane risk of bias tool); AMSTAR score 5/11.

Cystitis Prophylaxis

Muller et al. 2016:[20] systematic review of trials assessing nitrofurantoin for UTI prophylaxis
- controlled trials (N=17, n=511 patients); average nitrofurantoin prophylaxis duration 6 months (3-24 months)
  - nitrofurantoin vs. active comparator/placebo**:** one episode of interstitial pneumonia (diagnosed 37 months after initiation of nitrofurantoin 100 mg/d prophylaxis) which fully resolved after nitrofurantoin discontinuation
- observational trials (N=16, n=NR); population-level, single-arm cohort studies;

Comments nitrofurantoin duration NR; majority included trials actually studied both tx & prophylaxis population (see below).

	Case Definition	Data Source	Results	Comments
ANSM 2015, 2011[21,22]	Nitrofurantoin Rxs associated with AEs	Voluntary, national (France) pharmacovigilance database; 2005-14	**pulmonary reaction incidence** (type NR): -2005-11: 1 in 49,245 Rxs -2010-14: 1 in 20,408 Rxs	Unable to verify full report; voluntary program (may under-estimate incidence)

- Not included in Muller et al.: population-level cohort (single arm) based on national (Finland), pharmacovigilance data; 1976-85; no adverse pulmonary rxns reported in n=1,023 patients <16 yrs with 3 UTIs previous 6 months receiving nitrofurantoin prophylaxis (avg 2 courses/patient; mean course duration was 316 d).[23]

Price et al. 2016:[24] meta-analysis of RCTs (N=12, n=1063) assessing UTI prophylaxis
- nitrofurantoin (≥ 6 mos) for vs. active comparator: 1 case of pneumonitits (NR when diagnosed or prognosis, nitrofurantoin 100 mg HS/d prophylaxis x 9 mos was the studied regimen)[25]

Comments: majority of trials were conducted 1977-2007; 3/12 studies were rated as poor-fair quality; publication bias present (? presence of unpublished negative studies); AMSTAR score 9/11.

Cystitis Treatment & Prophylaxis

	Methodology	Results
DHMA 2015[26]	Design: population-level, single-arm cohort Case definition: patients with nitrofurantoin associated AEs Data source: voluntary, national (Denmark) pharmacovigilance database; 2004-13	n=229,635 nitrofurantoin users (≥ 1 Rx) n=31 users with nitrofurantoin-associated pulmonary fibrosis AE **pulmonary reaction incidence:** -pulmonary fibrosis: 1 in 7,408 users Note: unable to verify full report; voluntary program (may under-estimate incidence). Acute or subacute pulmonary rxn NR
Jick et al. 1989[10]	Design: single-arm cohort Case definition: pts **hospitalized** with pulmonary dx & nitrofurantoin Rx within previous 90 d Data source: health maintenance organization (Seattle), hospital & pharmacy databases; 1976-86	n=16,101 nitrofurantoin users (≥ 1 Rx) **n=4 users with nitrofurantoin-associated pulmonary AE** -cystitis tx: n= 3 acute rxn (46-74 yr, 7-19 d duration [report nitrofurantoin "1st use" but patient hx was not comprehensive]; all rxn resolved "promptly" after D/C) -cystitis prophylaxis: n=1 chronic rxn (65 yr, 1.5 yr duration/15 Rx refills) **pulmonary reaction incidence:** (subacute pulmonary reaction NR) -acute rxn: 1 in 5,000 users; chronic rxn (≥ 10 Rx): 1 in 750 users
D'Arcy et al. 1985[11]	Design: population-level, single-arm cohort Case definition: nitrofurantoin courses associated with AEs Data source: manufacturer database (data from literature, clinical studies, & voluntary reports from practitioners/ regulatory authorities); 1953-84	n=121,430,000 nitrofurantoin courses n=1,724 cases of nitrofurantoin-associated pulmonary AEs **pulmonary reaction incidence:** -all: 1 in 70,435 courses; acute: 1 in 106,705 courses; subacute: 1 in 5,519,545 courses; chronic: 1 in 433,349 courses; miscellaneous (rxn NR): 1 in 429,081 courses Note: incidence may be overestimated as study compared worldwide cases to US courses; however, may also be underestimated as some reliance on voluntary reports.

Holmberg et al. 1980[12]	Design: case series Case definition: AE associated with nitrofurantoin Data source: voluntary, national (Sweden) pharmacovigilance database; 1966-76	n=921 nitrofurantoin-associated AEs reports (86% ♀; 62 yr [0-95 yr]; 19% had previously received nitrofurantoin of which 55% had a previous nitrofurantoin-associated AE [type NR]) **n=447 nitrofurantoin-associated pulmonary AEs reports** -62% chronic/recurrent UTI, 4% asymptomatic bacteriuria, 34% NR; 75% hospitalized **Acute rxn**: n=398 (89%), median dose 200 mg/d (20-400 mg/d), 86% < 1 mos tx, age 59 yr; **fatal rxn**: n=2 (0.5%), regimen nitrofurantoin 150 mg/d x 1 d duration, n=1 previous nitrofurantoin hypersensitivity rxn **Chronic rxn**: n=49 (11%), median dose 100 mg/d (50-200 mg/d), 84% ≥ 1 month tx, age 68 yr; **fatal rxn**: n=4 (8%), regimen nitrofurantoin 100-150 mg/d x 4-11 yr duration

UNCERTAINTIES[1-6,16,27-29]

- **Diagnosis is challenging**, as clinical presentation is variable. Nitrofurantoin-associated pulmonary rxns are considered a diagnosis of exclusion.
  - Majority of patients are first given a diagnosis of pneumonia, myocardial infarction, pulmonary embolism, or pulmonary edema/congestive heart failure.[14]
- **Monitoring patients** for nitrofurantoin pulmonary toxicity reactions is recommended; however, recommendations are vague.[27]
  - If prescribing nitrofurantoin for cystitis treatment, instruct patient to report fever, change in breathing, more shortness of breath or cough.
  - If Rxing nitrofurantoin for recurrent cystitis prophylaxis, instruct pt to report change in breathing, more shortness of breath or cough and consider baseline & q 6 mos CXR or PFT. Reassess nitrofurantoin's indication at **6**-12 mos.
  - A patient developed pulmonary toxicity after 2.5 years of nitrofurantoin 50 mg HS prophylaxis therapy, and successfully sued a UK general practitioner's practice for failing to monitor for nitrofurantoin's side effects. The expert clinical pharmacologist at the claim proceeding recommended a CXR every 6 months for monitoring.[28,29]
- **If nitrofurantoin-associated pulmonary toxicity is suspected, discontinue nitrofurantoin immediately.**
  - Many reactions resolve with discontinuation of nitrofurantoin only; however, consider corticosteroids if severe reaction (hypoxia, severe respiratory sx), or no improvement after 24-72 h nitrofurantoin withdrawal.
  - Consider bronchodilator if bronchospasm is present.

AE adverse event **AHSM** Agencenationale du medicament et des produits de la santé **BID** twice daily **CT** computerized tomography **CXR** chest xray **DHMA** Danish Health and Medicines Authority **ESR** erythrocyte sedimentation rate **FDA** Food and Drug Act **h** hour **NR** not reported **PFT** pulmonary function test **PO** oral **pt** patient **QID** four times daily **RCT** randomized controlled trial **Rx** prescription **rxn** reaction **sx** symptoms **TMP/SMX** cotrimoxazole or sulfamethoxazole/trimethoprim **tx** treatment **US** United States **UTI** urinary tract infection **WBC** white blood count **yr** year

ACKNOWLEDGEMENTS: Contributors & Reviews: B Jensen BSP, L Kosar MSC BSP, L Regier BSP BA **Prepared By**: M LeBras, PharmD; Alecia Gauthier BSP

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Appendix 2: AMSTAR Checklist (for systematic reviews ± meta-analysis)

AMSTAR Checklist	Hutter et al. 2015	Muller et al. 2016	Price et al. 2016
1. 'A priori' design?	N	N	Y
2. Duplicate study selection & data extraction?	Y	Y	Y
3. Comprehensive literature search preformed?	N	N	Y
4. Status of publication (grey literature) used as an inclusion criterion?	N	N	Y
5. List of studies provided?	N	N	N
6. Characteristics of included studies provided?	Y	Y	Y
7. Scientific quality of included studies assessed?	Y	Y	Y
8. Scientific quality of included studied used appropriately in formulation conclusions?	Y	Y	Y
9. Methods used to combine findings appropriate?	Y	Y	Y
10. Likelihood of publication bias assessed?	N	N	Y
11. Conflict of interest included?	N	N	N
Total (/11)	5	5	9