Medicines Adverse Reactions Committee

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<tr><td>Meeting date</td><td>14 March 2019</td><td>Agenda item</td><td>3.2.4</td></tr>
<tr><td>Title</td><td colspan="3">Update on Nitrofurantoin Use in Renal Impairment</td></tr>
<tr><td>Submitted by</td><td>Medsafe Pharmacovigilance Team</td><td>Paper type</td><td>For advice</td></tr>
<tr><td>Active constituent
Nitrofurantoin</td><td colspan="3">Medicines
Nifuran - 50mg and 100mg tablets
Sponsors
W M Bamford & Co Ltd</td></tr>
<tr><td>Funding</td><td colspan="3">Fully funded by PHARMAC</td></tr>
<tr><td>Previous MARC meetings</td><td colspan="3">The use of nitrofurantoin in renal impairment has been discussed previously at the following meeting:
– 163rd Meeting — 10 September 2015
Nitrofurantoin use in renal impairment
The Committee considered that there was no public health need to increase access to nitrofurantoin and the contraindication for use should remain at a creatinine clearance of less than 60 mL/min.</td></tr>
<tr><td>International action</td><td colspan="3">– MHRA (September 2014): Nitrofurantoin now contraindicated in most patients with an estimated glomerular filtration rate (eGFR) of less than 45mL/min/1.73m^2.</td></tr>
<tr><td>Prescriber Update</td><td colspan="3">Pulmonary Reactions with Nitrofurantoin - May 2002
Nitrofurantoin - monitor lung function in long-term use - June 2006
Nitrofurantoin – Do the Benefits Outweigh the Risks? - June 2012
MARC's Remarks: September 2015 Meeting - December 2015
Nitrofurantoin – Not Suitable in Renal Impairment – December 2015
Medicine-induced Lung Disease - June 2016
Ghosts of Medicines Passed – June 2016</td></tr>
<tr><td>Schedule</td><td colspan="3">Prescription medicine</td></tr>
<tr><td>Usage data</td><td colspan="3">DataPharm (beta) shows the number of dispensings and the number of patients who received a dispensing of a subsidised nitrofurantoin product from a community pharmacy between 2013 and 2017.
<table>
<tr><th rowspan="2">Year</th><th colspan="2">Nitrofurantoin 50mg tablets</th><th colspan="2">Nitrofurantoin 100mg tablets</th></tr>
<tr><th>Patients</th><th>Dispensings</th><th>Patients</th><th>Dispensings</th></tr>
<tr><td>2013</td><td>32601</td><td>60581</td><td>18144</td><td>26352</td></tr>
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Advice sought	**The Committee is asked to advise:** – Whether the new evidence warrants a change to the current contraindication point for nitrofurantoin use in renal impairment (creatinine clearance [CrCl] <60mL/min). – If a change to the contraindication point is warranted, what the new cut-off for creatinine clearance (CrCl) should be. – How this issue should be communicated to healthcare professionals and consumers.

Contents

1.0 PURPOSE

The use of nitrofurantoin in renal impairment was discussed at the 163rd MARC meeting on 10 September 2015. The Committee reviewed the literature presented by Medsafe and considered that the contraindication for nitrofurantoin use should remain at a creatinine clearance (CrCl) of less than 60mL/min. A copy of the report presented at that meeting is attached as Annex 1.

Since then, Medsafe has become aware of newly published literature through the New Zealand Formulary (NZF) Editorial Advisory Board (EAB). As a result, we wish to provide the Committee with an update on this topic.

The advice sought from the Committee is whether there is sufficient evidence to warrant a change to the current contraindication point of CrCl <60mL/min, given the new information.

2.0 BACKGROUND

Previously in the United Kingdom, nitrofurantoin was contraindicated in patients with a creatinine clearance (CrCl) of less than 60 mL/min. It is now contraindicated in most patients with an eGFR of less than 45 mL/min. A short course of three to seven days may be used with caution in certain patients with an eGFR of 30 to 44 mL/min. Nitrofurantoin may be used in these patients with urinary tract infection (UTI) with suspected or proven multidrug resistant pathogens when the benefits of nitrofurantoin are considered to outweigh the risk of adverse effects.

Glomerular filtration rate (GFR) describes the flow rate of filtered fluid through the kidney and is a measure of kidney function. CrCl is the volume of blood plasma that is cleared of creatinine per unit time and is a useful measure for approximating the GFR. Normal kidney function is defined as levels above 90 mL/min, mild kidney disease as 60-89 mL/min with evidence of kidney damage, moderate kidney disease as 30-59 mL/min, severe kidney disease as 15-29 mL/min and kidney failure as less than 15 mL/min.

At the 163rd MARC meeting, the Committee discussed the differences between the Cockroft-Gault equation and eGFR (estimated glomerular filtration rate) in estimating renal function. The Cockroft-Gault equation estimates creatinine clearance from serum creatinine, age, gender, and body weight. eGFR is calculated using the Modification of Diet in Renal Disease equation which is based on age, serum creatinine, gender and ethnicity. The Committee mentioned there could be significant differences in the two values calculated with each of these equations in people at extremes of body size.

2.1 Nitrofurantoin

Nitrofurantoin is classified as a prescription only medicine. It was first approved for use in New Zealand in 1969 and is indicated for the prophylaxis and treatment of infections of the genitourinary tract due to susceptible bacteria.

Nitrofurantoin is readily absorbed following administration. The presence of food can further increase the availability as well as the tolerability.

Nitrofurantoin is reduced by bacterial flavoproteins to reactive intermediates which inactivate or alter bacterial ribosomal proteins and other macromolecules. As a result of such inactivations, the vital biochemical processes of protein synthesis, aerobic energy metabolism, DNA synthesis, RNA synthesis and cell wall synthesis are inhibited. Nitrofurantoin possesses advantages with regard to resistance problems, compared to some of the other medicines used in this area. This may be due to nitrofurantoin's broad-based mode of action, as the necessary multiple and simultaneous mutations of the target macromolecules would likely be lethal to the bacteria (Annex 2).

Approximately 75% of the absorbed dose is rapidly metabolised by the liver (glutathione s-reductase), but 25% is excreted in the urine unchanged. Tubular reabsorption of nitrofurantoin is pH

dependent, and reabsorption is promoted by acid urine (pH ≤ 5.5). Conversely, tubular reabsorption is decreased by alkaline urine, which results in an increased concentration of nitrofurantoin in the bladder (1).

Nitrofurantoin efficacy in lower urinary tract infections is dependent upon it being concentrated in the bladder. Due to the metabolism and excretion properties, blood plasma levels of nitrofurantoin in healthy subjects are low. In subjects with reduced renal function there may be more systemic accumulation and less urinary accumulation, which increases the risk of adverse effects and reduces the efficacy. It is for these reasons that nitrofurantoin is contraindicated in patients with a reduced renal function.

2.2 Data sheets

Table 1 below shows the renal function contraindications according to jurisdiction. A copy of the most recent New Zealand *Nifuran* data sheet is attached as Annex 2. Table 2 compares the dosage recommendations between New Zealand and the UK.

Table 1: Nitrofurantoin renal function contraindications according to jurisdiction

Jurisdiction/Regulator	Contraindications for nitrofurantoin use related to renal function
New Zealand (Medsafe)	Anuria, oliguria, or significant impairment of renal function (**CrCl <60mL/min** or clinically significant elevated serum creatinine) (Annex 2)
Australia (TGA)	Anuria and oliguria or extensive impairment of renal function (**CrCl <60mL/min** or clinically significant elevated serum creatinine) (2, 3).
US (FDA)	Anuria, oliguria, or significant impairment of renal function (**creatinine clearance under 60 mL per minute** or clinically significant elevated serum creatinine) (4, 5).
UK (MHRA)	Patients suffering from renal dysfunction with an **eGFR of less than 45 ml/minute**. However, nitrofurantoin may be used with caution as short-course therapy only for the treatment of uncomplicated lower urinary tract infection in individual cases with **an eGFR between 30-44 mL/min** to treat resistant pathogens, when the benefits are expected to outweigh the risks (6-8).

Table 2: Comparison of the New Zealand nitrofurantoin dose recommendations with the UK (immediate-release)

New Zealand (Medsafe) (Annex 2)	UK (MHRA) (7)
Acute, Uncomplicated Urinary Tract Infections (acute cystitis) Adults: Usual dose 50-100 mg four times daily for 7 days Children 1 month- 12 years: 5-7 mg/kg body weight per 24 hours, given in four divided doses	**Acute Uncomplicated Urinary Tract Infections** Adults: 50mg four times daily for seven days. Children and infants over three months of age 3mg/kg/day in four divided doses for seven days **Severe Chronic Recurrence (UTIs)** Adults: 100mg four times daily for seven days

Prophylactic Therapy	Long-Term Suppressive Therapy
Adults: Usual dose 50-100 mg at bedtime Children 1 month - 12 years: 1 mg/kg body weight per 24 hours, given in a single dose or in two divided doses	Adults: 50-100mg once a day Children and Infants over three months of age 1mg/kg/day once a day **Prophylaxis following surgical procedures:** Adults: 50mg four times daily for the duration of the procedure and for the 3 days thereafter

2.3 CARM data

2.3.1 Nitrofurantoin – Spontaneous reports in New Zealand – 1965 to 31 December 2018

The Centre for Adverse Reactions Monitoring (CARM) has received 386 adverse reaction reports, containing 748 reactions, where nitrofurantoin was considered as a suspect medicine regardless of the level of causality (since database inception). Of these reports, 44% (n=170) had an onset time of less than one week, 15% (n=58) less than one month and 33% (n=127) more than one month. The duration to onset was unknown in 8% of reports (n=31). The data does not provide information on dose, frequency or patient renal function.

Table 3 shows the onset time of the reaction by age group. This table shows that although the incidence of adverse reactions increases with increasing age, these still occur amongst all age groups. It is not known if nitrofurantoin was still being taken when the reactions occurred or whether nitrofurantoin was being taken for acute infection or long-term prophylaxis. For example, the patient may have taken a 5 day course, but the reaction started one month later or the reaction occurred within the first week of long-term, lower daily dose, prophylactic therapy.

Table 4 shows the data that was presented at the 2015 MARC meeting for comparison.

Table 3: Reaction onset by age group (1965 - 31 December 2018)

Age	< 1 week	< 1 month	> 1 month	Unknown	Total
< 20 years	4	1	0	0	**5**
20 – 29 years	11	5	1	3	**20**
30 – 39 years	15	6	5	0	**26**
40 – 49 years	16	4	7	3	**30**
50 – 59 years	42	6	15	2	**65**
60 – 69 years	28	13	28	6	**75**
> 70 years	54	22	70	17	**163**
Unknown	0	1	1	0	**2**
Total	**170**	**58**	**127**	**31**	**386**

Table 4: Reaction onset by age group (data presented at the September 2015 MARC meeting)

Age	< 1 week	< 1 month	> 1 month	Unknown	Total
< 20 years	4	1	0	0	**5**
20 – 29 years	10	4	1	0	**15**
30 – 39 years	14	6	4	0	**24**
40 – 49 years	13	4	7	3	**27**
50 – 59 years	33	6	14	3	**56**
60 – 69 years	23	13	23	6	**65**
> 70 years	37	18	57	14	**126**
Unknown	0	1	0	0	**1**
Total	**134**	**53**	**106**	**26**	**319**

2015 data: 42% of reports (n=134) had an onset time < 1 week, 17% (n=53) less than one month and 33% (n=106) more than one month. The duration to onset was unknown in 8% of reports (n=26).

Comment: Most of the new reports (n=67) received from 2015-2018 describe ADR onset of < 1 week (n= 36) or > 1 month (n=21). Over half of the new reports were in patients over the age of 60 (n=47).

Reactions were also grouped according to the WHO terminology, system organ class (SOC). Table 5 shows the distribution of reactions according to SOC by onset time, where each SOC was counted only once per report. For example, if there were two reactions from one report from the same SOC then this was counted only once and if there was a report with reactions from more than one SOC, the report was counted one time for each SOC (n=626).

Table 6 shows the data that was presented to the Committee in 2015 for comparison.

Table 5: Reaction type (System Organ Class)* by onset time (1965-December 2018)

System Organ Class	< 1 week	< 1 month	> 1 month	Unknown	Total
Alimentary	47	9	5	3	**64**
Cardiovascular	19	5	1	3	**28**
Collagen Disorders	0	0	1	0	**1**
Endocrine/Metabolic	2	2	2	0	**6**
Haematological	7	5	1	1	**14**
Liver	10	6	24	4	**44**
Musculoskeletal	11	5	1	2	**19**
Nervous System	24	11	26	4	**65**
Others	40	16	7	7	**70**
Procedure Related	0	0	7	0	**7**
Psychiatric Changes	13	4	1	2	**20**
Resistance Mechanism Disorders	2	0	0	0	**2**
Respiratory	37	25	76	16	**154**
Skin and Appendages	85	19	7	6	**117**
Special Senses	5	0	0	1	**6**
Urinary	2	2	5	0	**9**
Total	**304**	**109**	**164**	**49**	**626**

*According to WHO-ART terminology

This table shows that the distribution of reaction onset time was varied and depended on the type of reaction grouping. For example, there were 117 reports with reactions in the skin and appendages SOC; however the majority (n=85) occurred within the first week. The time to reaction onset distribution was different within the respiratory SOC. There was a more even split between reactions that occurred acutely compared with those that occurred with ongoing nitrofurantoin use. This reflects the difference in pulmonary reactions (both acute hypersensitivity and chronic infiltration) that occur with nitrofurantoin use.

Individually, the reactions most frequently reported included rash (n=54), dyspnoea (n=37), fever (n=33), pulmonary fibrosis (n=31), vomiting (n=31), nausea (n=23), coughing (n=22), interstitial lung disease (n=22), pneumonia interstitial (n=18), headache (n=17), neuropathy (n=15), urticaria (n=13), pneumonitis (n=11), pruritus (n=11), rash maculopapular (n=11), rigors (n=11), hepatic function abnormal (n=10), peripheral neuritis (n=10) and pulmonary infiltration (n=10).

The respiratory, skin and appendages, nervous system and alimentary SOC groups were the SOC groups with the most reactions and the most commonly reported individual reactions were representative of this.

Table 6: Reaction type (System Organ Class)* by onset time (data presented at the September 2015 MARC meeting)

System Organ Class	< 1 week	< 1 month	> 1 month	Unknown	Total
Alimentary	37	9	4	2	**52**
Cardiovascular	15	4	1	3	**23**
Collagen Disorders	0	0	1	0	**1**
Endocrine/Metabolic	1	1	2	0	**4**
Haematological	3	4	1	1	**9**
Liver	7	5	21	4	**37**
Musculoskeletal	10	4	0	2	**16**
Nervous System	19	9	25	2	**55**
Others	33	13	7	7	**60**
Procedure Related	0	0	2	0	**2**
Psychiatric Changes	10	3	1	3	**17**
Resistance Mechanism Disorders	1	0	0	0	**1**
Respiratory	33	23	61	14	**131**
Skin and Appendages	65	27	6	4	**92**
Special Senses	4	0	0	1	**5**
Urinary	2	1	3	0	**6**
Total	**240**	**93**	**135**	**43**	**511**

*According to WHO-ART terminology

2015 data for comparison: Individually, the reactions most frequently reported included rash (n=47), dyspnoea (n=32), fever (n=29), vomiting (n=26), pulmonary fibrosis (n=26), nausea (n=20), coughing (n=20), pneumonia interstitial (n=16), neuropathy (n=15), interstitial lung disease (n=15), headache (n=14), rigors (n=11) and peripheral neuritis (n=10).

Comment: Between 2015 and the end of 2018, the SOCs that were reported most frequently were: Skin and Appendages (25 reports), Respiratory (23 reports), Alimentary (12 reports), CNS (10 reports). Of the 25 new reports that contained a skin ADR, 20 had an onset date <1 week. Of the 23 new reports that contained a respiratory ADR, 15 had an onset date of >1month.

3.0 SCIENTIFIC INFORMATION

3.1 Literature discussed at the 163rd MARC meeting

In 2015, the MARC reviewed a number of papers related to nitrofurantoin and renal impairment and/or adverse reactions. These are discussed below. For a full summary of the data, please refer to Annex 1.

3.1.1 Oplinger and Andrews (2013) – Nitrofurantoin contraindication in patients with creatinine clearance below 60mL/min: Looking for the evidence

This article reviewed prior studies that measured urinary nitrofurantoin and/or clinical outcomes from 1965 until June 2012. These studies included: *Sachs*, *Schlegel*, *Lippman*, *Felts,* and *Bains et al* (3.1.2).

Table 1 summarises some of the findings from these studies.

Conclusion: The authors concluded that the contraindication to use nitrofurantoin in patients with CrCl < 60mL/min is based on early studies. Most of these studies had a small sample size, lack of methodology information, and variable doses and durations of use. Based on the *Bain* chart review, the authors considered it reasonable to consider a cut-off of CrCl 40mL/min when sensitivity data support nitrofurantoin use for short-term treatment (one week or less) of uncomplicated UTI.

Table 1: Summary of nitrofurantoin urinary excretion data

Reference	Pts./Dosage	Nitrofurantoin Outcome	CrCl (mL/min)			
			<20	20-40	41-60	>60
Sachs (1968)[14]	N = ~18 with CrCl ≤60 mL/min)[a] 100 mg orally (1 dose)	Amount (mg), 10-hour urine collection Maximum urine concentration (mg/dL), 10-hour collection	0-5 <5	0-9 <5 to <10	0-25 <5-15	22-50 <5-25
Schlegel (1967)[16]	N = ~10 with CrCl ≤60 mL/min)[a] 100 mg orally (repeated doses)	Amount (mg), 24-hour urine collection Maximum urine concentration (mg/dL), 24-hour collection	<50 <5	75-150 <5	25-150 <5	100-250 <5
Lippman (1958)[17]	N = 8 considered "azotemic" 50 mg orally (repeated doses)	Mean (range) maximum urine concentration (mg/dL)[b]	In "azotemia" (SCr 1.88-7.8 mg/dL) collections 1 and 3: 2 (0-5) In "normal" renal function (SCr 0.66-1.26 mg/dL) collection 2: 11 (4-23)			
Felts (1971)[18]	N = 6 with "renal insufficiency" 100 mg orally (single dose)	Mean (range) maximum urine concentration (mg/dL), 6-hour collection	In "normal" renal function (CrCl ≥80 mL/min): 7.4 (0.6-10.6)[c] In "renal insufficiency" CrCl <20 mL/min: 0.6 CrCl 20-50 mL/min: 1.6 CrCl 95 mL/min[d]: 2.7			

CrCl = creatinine clearance; SCr = serum creatinine.
[a]Data not provided; estimated from graphical representations.
[b]There were 3 urine collections at 5-hour intervals from 7 AM to 10 PM (collections 1-3) and a 4th 9-hour collection from 10 PM to 7 AM. The highest concentration reported in any of the 4 collection times was selected.
[c]One individual (CrCl >100 mL/min) with minimal nitrofurantoin excretion.
[d]85-year-old pt. included in this group.

3.1.2 Bains et al. (2009) – A retrospective review assessing the efficacy and safety of nitrofurantoin in renal impairment

Study type: Retrospective review of medical records of all patients with suspected UTI who had received nitrofurantoin from 2004 to 2008, in the Southern region of the Vancouver Island Health Authority (VIHA), Canada.

Aims: To assess the efficacy and safety of nitrofurantoin in patients with renal impairment (eGFR ≤50 mL/min) compared to controls (eGFR>50 mL/min) using patient records from acute and long-term care hospitals.

Inclusion/exclusion criteria: Patients had to be in hospital for at least 14 days after antibiotic treatment was finished. Patients were excluded if treatment was stopped for any reason aside from therapy failure.

Study endpoints: Primary outcome: Cure (clinical and/or microbiological). Clinical cure = treatment discontinuation after an appropriate course of antibiotics (between 5 to 10 days) with no other UTI antibiotics initiated within 14 days and no UTI symptoms. Microbiological cure = when a repeat negative culture was documented.

Secondary outcome: Adverse events, when experienced by the patient or if the patient received treatment for these events up to 7 days following UTI treatment.

Limitations:

- Retrospective study – may be inadequate documentation of ADRs or treatment failure.
- There were not enough patients for significant power (80%), where 200 patients in each arm were needed.
- The study population selection was biased by the required hospitalisation time after the end of treatment and UTIs were suspected, not microbiologically confirmed.
- The mean CrCl in the renal impairment group was 40mL/min, therefore extrapolation of results to patients with severe renal impairment is not possible.

Results: A total of 356 patients met the inclusion criteria. Patient demographics are presented below in Table 1, according to different eGFR calculations.

Table 1: Patient data with respect to renal function*

	MCG[11]		Elderly-Adjusted MCG[11]		MDRD[12]	
	Control*	Renal impairment	Control	Renal impairment	Control	Renal impairment
Patients, *n*	234	122	163	193	284	72
Mean age in years (range)	73 (4–96)	86 (69–103)	67 (4–89)	86 (69–103)	76 (4–98)	83 (43–103)
Male, % (*n*)	29 (67)	16 (19)	39 (64)	11 (22)	29 (82)	6 (4)
Mean creatinine clearance in mL/min (range)	83 (51–387)	40 (15–50)	92 (51–387)	48 (15–50)	76 (51–406)	36 (19–50)
Diabetic, % (*n*)	17 (40)	15 (18)	21 (34)	12 (24)	17 (48)	14 (10)
Postherpetic neuralgia, *n*	1	1	0	2	1	1
Any previous neuropathy, *n*	30	12	21	21	33	9
Any previous pulmonary reaction, *n*	2	0	2	0	2	0
Sulfasalazine, *n*	0	0	0	0	0	0
Amiodarone, *n*	2	4	1	5	3	3
Antineoplastics, *n*	4	0	2	2	4	0
Propranolol, *n*	1	1	1	1	1	1
Hydralazine, *n*	1	1	1	1	1	1

*Control group = estimated GFR >50 mL/min; renal impairment group = estimated GFR ≤50 mL/min.

*MCG=Modified Cockcroft-Gault equation; MDRD=Modification of Diet in Renal Disease

The cure rates did not vary significantly between the two cohorts using any of the eGFR equations, as shown in table 2. Rates of ADRs are shown in Table 3.

Table 2: Clinical cure rates with respect to renal function

	MCG[11]		Elderly-Adjusted MCG[11]		MDRD[12]	
	Control†	Renal impairment	Control	Renal impairment	Control	Renal impairment
Cure, % (95% CI)	78 (73–84)	71 (63–79)	76 (69–83)	75 (69–81)	76 (71–81)	72 (62–83)
No cure, % (95% CI)	22 (16–27)	29 (21–37)	24 (17–31)	25 (19–31)	24 (19–29)	28 (17–38)

*Both clinical and microbiological cure rates were examined. However, evidence supporting microbiological cure was not available in most instances. †Control group = estimated GFR >50 mL/min; renal impairment group = estimated GFR ≤50 mL/min.

Table 3: Reported minor adverse events with respect to renal function

	MCG[11]		Elderly-Adjusted MCG[11]		MDRD[12]	
	Control*	Renal impairment	Control	Renal impairment	Control	Renal impairment
Gastrointestinal disturbance or headache,† % (no.)	8 (18)	7 (9)	9 (15)	6 (12)	7 (21)	8 (6)

*Control group = estimated GFR >50 mL/min; renal impairment group = estimated GFR ≤50 mL/min.
†Experienced or received treatment for the condition during UTI therapy.

3.1.3 Singh et al. (2015) – Kidney function and the use of nitrofurantoin to treat urinary tract infection in older women

Study type: Population based, retrospective cohort study (June 2002 – March 2013) Ontario, Canada

Aim(s): To compare the risk of treatment failure for UTI between patients treated with nitrofurantoin and those treated with other indicated antibiotics (ciprofloxacin, norfloxacin or co-trimoxazole)

Inclusion criteria: Women, ≥65 years, relatively low eGFR (median eGFR 38mL/min/1.73m^2). This cohort was compared with a cohort of women with relatively high eGFR (median eGFR 69mL/min/1.73m^2)

Measures of treatment failure: Two – receipt of a second antibiotic indicated for UTI and hospital presentation with a UTI in the 14 days following prescription of an antibiotic, as treatment success was not directly recorded in the datasets.

Potential confounders adjusted for: age, year of cohort entry, rural residence, duration of initial antibiotic prescription (≤ 7 days vs > 7 days), number of antibiotic prescriptions in the previous five years, number of unique medications and presence of dementia, stroke, diabetes and urinary incontinence.

Results: There were 9,233 women with relatively low eGFR and 182,634 women with relatively high eGFR identified who were prescribed one of the four study drugs. Baseline characteristics were similar across the four antibiotic groups in each of the two cohorts.

Lower eGFR patients

In patients with relatively low eGFR, receipt of ciprofloxacin or norfloxacin was associated with lower likelihood of receiving a second antibiotic during the follow-up period relative to nitrofurantoin. Ciprofloxacin or norfloxacin were also associated with lower likelihood of a hospital encounter relative to nitrofurantoin. Receipt of co-trimoxazole was associated with a lower incidence of both outcomes relative to nitrofurantoin, but neither comparison was statistically significant, as shown in Table 1 below.

Higher eGFR patients

The patterns were similar for patients with relatively high eGFR. Patients with relatively high eGFR had a lower incidence of treatment failure, as shown in Table 1 below.

Subgroup analysis

In a subgroup analysis of 48,195 women whom baseline serum creatinine values were available – the results were similar to the results of the primary analysis, as shown in Table 2.

These patients were divided into three groups according to GFR: <40mL/min/1.73m^2, 40-60mL/min/1.73m^2 and >60mL/min/1.73m^2.

The rate of treatment failure was higher among patients who received nitrofurantoin than among those who received other antibiotics, regardless of the patient's eGFR, as shown in Table 2.

Table 1: Treatment failure in patients with relatively low and relatively high eGFR

Indicator of failure* and drug	No. with event/ total no. of patients (%)		OR (95% CI)	
			Unadjusted	Adjusted†
Relatively low eGFR‡				
Second prescription				
Nitrofurantoin	516/3 739	(13.8)	1.00	1.00
Ciprofloxacin	130/1 989	(6.5)	0.44 (0.36–0.53)	0.43 (0.35–0.53)
Norfloxacin	133/2 032	(6.5)	0.44 (0.36–0.53)	0.44 (0.36–0.54)
TMP–SMX	184/1 463	(12.6)	0.90 (0.75–1.08)	0.92 (0.77–1.10)
Hospital encounter with UTI				
Nitrofurantoin	95/3 739	(2.5)	1.00	1.00
Ciprofloxacin	21/1 989	(1.1)	0.41 (0.25–0.66)	0.40 (0.25–0.64)
Norfloxacin	24/2 032	(1.2)	0.46 (0.29–0.72)	0.45 (0.28–0.71)
TMP–SMX	31/1 463	(2.1)	0.83 (0.55–1.25)	0.81 (0.53–1.22)
Relatively high eGFR§				
Second prescription				
Nitrofurantoin	7 759/70 758	(11.0)	1.00	1.00
Ciprofloxacin	1 713/29 095	(5.9)	0.51 (0.48–0.54)	0.50 (0.47–0.53)
Norfloxacin	2 734/45 116	(6.1)	0.52 (0.50–0.55)	0.54 (0.52–0.57)
TMP–SMX	3 683/37 665	(9.8)	0.88 (0.84–0.92)	0.93 (0.89–0.97)
Hospital encounter with UTI				
Nitrofurantoin	863/70 758	(1.2)	1.00	1.00
Ciprofloxacin	241/29 095	(0.8)	0.68 (0.59–0.78)	0.65 (0.56–0.75)
Norfloxacin	272/45 116	(0.6)	0.49 (0.43–0.56)	0.51 (0.44–0.58)
TMP–SMX	412/37 665	(1.1)	0.90 (0.80–1.01)	0.93 (0.83–1.05)

Note: CI = confidence interval, eGFR = estimated glomerular filtration rate, OR = odds ratio, TMP–SMX = trimethoprim–sulfamethoxazole, UTI = urinary tract infection.
*The follow-up time was the 14 days following antibiotic dispensing.
†Analyses were adjusted for age, year of cohort entry, rural residence, duration of initial antibiotic prescription (≤ 7 d v. > 7), prior number of antibiotic prescriptions, prior number of urine cultures, number of unique medications, dementia, stroke, diabetes mellitus and urinary incontinence.
‡Cohort with relatively low eGFR: the algorithm of database codes identified patients with a median eGFR of 38 (IQR 27–52) mL/min per 1.73 m^2.[19]
§Cohort with relatively high eGFR (absence of chronic kidney disease): the algorithm of database codes identified patients with a median eGFR of 69 (IQR 56–82) mL/min per 1.73 m^2.[19]

Table 2: Treatment failure in a subpopulation with serum creatinine laboratory values

Indicator of Failure* and Drug	No. with event/ total no. patients (%)	Odds Ratio (95% CI)	
		Unadjusted	Adjusted†
eGFR <40 mL/min per 1.73m^2			
Second Antibiotic Prescription			
Nitrofurantoin	160/1 161 (13.8)	1.00	1.00
Ciprofloxacin	39/669 (5.8)	0.39 (0.27 to 0.56)	0.37 (0.26 to 0.54)
Norfloxacin	61/906 (6.7)	0.45 (0.33 to 0.62)	0.45 (0.33 to 0.62)
TMP-SMX	57/532 (10.7)	0.75 (0.54 to 1.04)	0.77 (0.55 to 1.06)
Hospital Encounter with a UTI			
Nitrofurantoin	23/1 161 (2.0)	1.00	1.00
Ciprofloxacin	12/669 (1.8)	0.90 (0.45 to 1.83)	0.82 (0.40 to 1.67)
Norfloxacin	8/906 (0.9)	0.44 (0.20 to 0.99)	0.44 (0.19 to 0.99)
TMP-SMX	13/532 (2.4)	1.24 (0.62-2.47)	1.18 (0.59 to 2.38)
eGFR 40-60 mL/min per 1.73m^{-2}			
Second antibiotic prescription			
Nitrofurantoin	532/4 251 (12.5)	1.00	1.00
Ciprofloxacin	112/1 779 (6.3)	0.47 (0.38 to 0.58)	0.47 (0.38 to 0.58)
Norfloxacin	196/3 068 (6.4)	0.48 (0.40 to 0.57)	0.49 (0.42 to 0.59)
TMP-SMX	203/1 883 (10.8)	0.85 (0.71 to 1.00)	0.88 (0.74 to 1.05)
Hospital Encounter with a UTI			
Nitrofurantoin	56/4 251 (1.3)	1.00	1.00
Ciprofloxacin	22/1 779 (1.2)	0.94 (0.57 to 1.54)	0.94 (0.57 to 1.55)
Norfloxacin	29/3 068 (1.0)	0.72 (0.46 to 1.12)	0.79 (0.50 to 1.25)
TMP-SMX	21/1 883 (1.1)	0.85 (0.51 to 1.40)	0.89 (0.54 to 1.49)
eGFR >60 mL/min per 1.73m^{-2}			
Second antibiotic prescription			
Nitrofurantoin	1 596/14 207 (11.2)	1.00	1.00
Ciprofloxacin	331/5 251 (6.3)	0.53 (0.47 to 0.60)	0.52 (0.46 to 0.59)
Norfloxacin	557/8 744 (6.4)	0.54 (0.49 to 0.59)	0.56 (0.51 to 0.62)
TMP-SMX	633/5 744 (11.0)	0.98 (0.89 to 1.08)	1.03 (0.94 to 1.14)
Hospital Encounter with a UTI			
Nitrofurantoin	157/14 207 (1.1)	1.00	1.00
Ciprofloxacin	34/5 251 (0.7)	0.58 (0.40 to 0.85)	0.56 (0.38 to 0.81)
Norfloxacin	39/8 744 (0.5)	0.40 (0.28 to 0.57)	0.42 (0.29 to 0.60)
TMP-SMX	55/5 744 (1.0)	0.87 (0.64 to 1.18)	0.91 (0.66 to 1.24)

eGFR= estimated glomerular filtration rate. CI= confidence interval. TMP-SMX= trimethoprim-sulfamethoxazole. UTI= urinary tract infection.
*The follow-up time was the 14 days following antibiotic dispensing.
†Analyses adjusted for age, year of cohort entry, rural residence, duration of initial antibiotic prescription, prior number of antibiotic prescriptions, prior number of urine cultures, number of unique medications, dementia, stroke, diabetes, and urinary incontinence.

3.1.4 Gilbert (2006) – Urinary tract infections in patients with chronic renal insufficiency

Aim: To determine which antibiotics were and were not appropriate in UTI patients with chronic renal insufficiency.

Results: Nitrofurantoin at the usual recommended dosage did not reach minimal inhibitory urinary drug concentration below a CrCl of 20mL/min. As little or no nitrofurantoin is excreted in the urine, nitrofurantoin should not be used in these patients.

It was noted that the urine concentration of trimethoprim remains high even in marked renal insufficiency.

Comment: Drug levels in patients with CrCl over 20mL/min up to 60mL/min were not ascertained. The abstract suggests that nitrofurantoin has inadequate concentrations in patients with CrCl < 50mL/min, but the literature used in the text does not show this.

3.1.5 Holmberg et al. (1980) - Adverse reactions to nitrofurantoin: Analysis of 921 reports

Study type: Analysis of ADR reports to nitrofurantoin (to the Swedish ADR Committee) from 1966-76

Aim: To determine the types of adverse reactions experienced

Report demographics: Women made up 86% of patients. Median age was 62 years (mean 59 years)

Results: Pulmonary reactions, particularly acute pulmonary hypersensitivity, made up almost half of all ADR reports, followed by allergic reactions. Fatalities were reported, as shown in Table 1. The doses at which ADRs occurred, as well as the treatment stop date were not reported.

Table 1: Adverse reactions to nitrofurantoin, 1966-1976

		Total Patients		Hospitalized Patients		Fatal Cases	
		No.	%	No.	%	No.	%
Pulmonary reactions		447	48	337	75		
Acute pulmonary hypersensitivity	398					2	0.5
Chronic interstitial pneumonitis	49					4	8
Allergic reactions		384	42	243	63	—	—
Liver damage		50	6	38	76	1	2
Blood dyscrasias		20	2	20	100	4	20
Neuropathy		20	2	13	65	—	—
		921	100	651	71	11	1

While patients had more than one symptom, fever was the most common initial symptom that triggered the patient to seek medical advice, as shown in Table 2.

Table 2: Initial symptoms in nitrofurantoin reactions (one or more symptoms per patient)

Symptoms	No.	%
Fever (≥38°C)	646	70
Dyspnea	312	34
Exanthema	261	28
Dry cough	241	26
Fatigue	106	12
"Flu"	87	9
Cyanosis	36	4
Jaundice	29	3
Weight loss	22	2
Total	1,740*	

* Symptoms in 921 patients (1.9 per patient).

The duration of treatment with nitrofurantoin before symptom onset varied considererably. The majority (697 patients) received treatment for less than 1 month, as shown in Table 3. Short-term treatment predominated among those with acute pulmonary and allergic reactions, wheras chronic pulmonary reactions and liver damage were receiving long-term treatment.

Table 3: Duration of last continuous therapy before onset of symptoms, number of patients

Type of Reactions	Duration				
	<1 mo	1-12 mo	>12 mo	Unknown	Total
Pulmonary, acute	343 (86)*	10	5	40	398
Pulmonary, chronic	1	18	23 (47)	7	49
Allergic	311 (81)	13	—	60	384
Liver damage	23 (46)	6	12	9	50
Blood dyscrasias	10 (50)	3	1	6	20
Neuropathy	9 (45)	7	1	3	20
Totals	697 (76)	57 (6)	42 (5)	125 (14)	921 (100)

* The most common period of treatment in each type of reaction is indicated by a percentage figure (figures in parentheses).

172 patients knew they had been given one or more courses of nitrofurantoin prior to the present episode. Just over half of these patients had reported previous adverse reactions to nitrofurantoin. It was noted that the reactions in the lungs and skin, have the characteristics of an acute hypersensitivity reaction, with many patients sensitised by previous treatment.

3.1.6 Geerts et al. (2013) - Ineffectiveness and adverse events of nitrofurantoin in women with urinary tract infection and renal impairment in primary care

Study type: Retrospective cohort study (conducted in the Netherlands)

Aim: To determine whether ineffectiveness & the occurrence of ADRs during nitrofurantoin treatment were dependent on renal function.

Cohorts: Two cohorts – female nitrofurantoin OR female trimethoprim users, with and without known CrCl values.

Outcomes: Ineffectiveness – defined as the start of a second antibacterial for treatment of a UTI within one month after the start of a course of nitrofurantoin. Occurrence of serious ADRs leading to hospitalisation within 90 days.

Potential confounders controlled for: age, anti-bacterial treatment duration, blood glucose-lowering medicine use, immunosuppressant use, urinary antispasmodic use, medicines use in cognitive impairment.

Results:

Although there was a trend for higher incidence densities for ineffectiveness with declining renal function with nitrofurantoin use, the association was not statistically significant. There was no trend observed with trimethoprim use, as shown in Table 1.

Table 1: Association between renal impairment and ineffective antibacterial treatment

eGFR (ml/min/ 1.73 m^2)	Second antibacterial, *n* (%)	Follow-up time (person-days)	Incidence density (per 1,000 person-days)	Crude HR (95 % CI)	Adjusted HR[a] (95 % CI)
Nitrofurantoin					
>80	291 (15.7)	49,241	5.91	1.00 (Reference)	1.00 (Reference)
50–80	314 (17.0)	48,068	6.53	1.10 (0.94–1.29)	0.92 (0.78–1.08)
30–49	35 (21.1)	4,191	8.35	1.41 (0.99–2.00)	1.06 (0.74–1.51)
10–29	6 (30.0)	456	13.16	2.12 (0.94–4.75)	1.57 (0.70–3.52)
<10	0 (0)	30	NA	NA	NA
Unknown	2,431 (13.9)	46,7318	5.20	0.89 (0.78–1.00)	0.90 (0.79–1.01)
Overall	3,077 (14.4)	569,304	5.40		
Trimethoprim					
>80	94 (16.0)	15,537	6.05	1.00 (Reference)	1.00 (Reference)
50–80	114 (19.1)	15,315	7.44	1.22 (0.93–1.60)	1.15 (0.87–1.51)
30–49	14 (18.9)	1,889	7.41	1.20 (0.68–2.10)	1.06 (0.60–1.88)
10–29	0 (0.0)	240	NA	NA	NA
<10	0 (0)	30	NA	NA	NA
Unknown	1,092 (16.4)	174,811	6.25	1.03 (0.84–1.27)	1.03 (0.83–1.27)
Overall	1,314 (16.6)	207,822	6.32		

HR, Hazard ratio; 95 % CI, 95 % confidence interval; NA, data not available

[a]Ajusted for age and use of blood glucose-lowering drugs

The risk of adverse events leading to hospitalisation was statistically significantly higher in nitrofurantoin users with renal impairment compared with those with adequate renal function, as shown in Table 2. Pulmonary reactions and blood dyscrasias were the reactions observed.

Table 2: Association between renal impairment and serious adverse events

eGFR (ml/min/1.7 m^2)	Adverse event, *n* (%)	Follow-up time (person-days)	Incidence density (per 1,000 person-days)	Crude HR (95 % CI)	AdjustedHR (95 % CI)[b]
Nitrofurantoin					
≥50	13 (0.35)	332,399	0.04	1.00 (Reference)	1.00 (Reference)
<50	4 (2.14)	16,618	0.24	6.14 (2.00–18.83)	4.13 (1.31–13.09)
Unknown	17 (0.10)	1,567,746	0.01	0.28 (0.14–0.57)	0.35 (0.17–0.73)
Overall	34 (0.16)	1,916,763	0.02		
Trimethoprim					
≥50	0 (NA)	106,740	NA	1.0 (Reference)	1.00 (Reference)
<50	0 (NA)	7,470	NA	NA	NA
Unknown	8 (0.12)	598,572	0.01	NA	NA
Overall	8 (0.10)	712,782	0.01		

[a] Adverse events during subsequent hospital admissions within 90 days after the start of a course of nitrofurantoin treatment: pulmonary reactions (n=33) and blood dyscrasias (n=1). Adverse events after the start of a course of trimethoprim treatment: pulmonary reactions (n=8)

[b] Adjusted for age

3.2 New published literature

A PubMed literature search using the search terms 'nitrofurantoin' and 'renal impairment' or 'kidney function' yielded six relevant papers and one abstract (*Loh et al*), published after the discussion at the September 2015 MARC meeting.

Five papers were retrospective studies (including the abstract), one paper was a systematic review of safety and efficacy of nitrofurantoin in UTI prophylaxis (*Muller et al*) and one paper was a review article (*Hoang et al*) that discussed the results of *Geerts et al* and *Bains et al*, shown in section 3.1.

The information in these seven articles is detailed below in order of publication year. Please find the papers attached as Annexes 3-9.

3.2.1 Ahmed et al (2018) - Risk of adverse outcomes following urinary tract infection in older people with renal impairment: Retrospective cohort study using linked health record data (Annex 3)

3.2.1.1 Methods

This was an English retrospective cohort study using linked health record data. The aim of this study was to determine the risk of adverse outcomes in patients aged ≥65 years presenting to primary care with a UTI, by estimated glomerular filtration rate (eGFR) and empirical prescription of nitrofurantoin versus trimethoprim. Data was collected using the Clinical Practice Research Datalink (CPRD).

Inclusion criteria

Patients were eligible for inclusion if, between 1 January 2010 and 31 December 2016 if:

- their data were of the quality required by the Clinical Practice Research Datalink (CPRD)
- they were ≥65 years old and eligible for data linkage

Only patients registered with practices that had consented to data linkage would have linked hospital and death registry data.

Exclusion criteria

Patients were excluded if they:

- were temporary residents
- had periods during their registration with the practice for which CPRD was unable to collect data, potentially leading to incomplete exposure/ event capture.

Identification of eligible patients

Eligible patients were identified with a Read code indicating an incident primary care presentation with a suspected UTI, a prescription code indicating same-day empirical prescribing of a relevant antibiotic, and a creatinine record in the preceding 24 months.

The authors defined `incident' as a presentation without a previous consultation with a UTI-related Read code, or trimethoprim or nitrofurantoin prescription in the preceding 90 days. We used the first incident episode during each patient's follow-up period. We excluded UTI episodes with a hospital discharge in the preceding 14 days to exclude hospital acquired infections.

Exposures

The authors used the most recent serum creatinine value recorded in the 24 months preceding the incident UTI and data for patient age, gender, and ethnicity to calculate an eGFR as per the Modification of Diet in Renal Disease (MDRD) Study equation.

The authors categorised eGFRs as: ≥60 mL/min/1.73 m^2, 45-59 mL/min/1.73 m^2, 30-44 mL/min/1.73 m^2, 15-29 mL/min/1.73 m^2, and <15 mL/min/1.73 m^2.

The authors used those with an eGFR ≥60 mL/min/1.73 m^2 as the reference and compared rates of adverse outcomes against the four other eGFR categories. We used the recorded empirical antibiotic prescription as the exposure variable to compare risk of adverse outcomes between patients with eGFRs <60 mL/ minute/1.73 m^2 prescribed trimethoprim versus nitrofurantoin.

Outcomes

The authors assessed the impact of exposures on the following adverse outcomes for patients empirically treated in primary care for an incident suspected UTI:

- Reconsultation for urinary symptoms and a same-day antibiotic prescription within 14 days following the incident UTI, as a proxy for treatment nonresponse, ascertained through Read and prescription codes recorded in primary care records.
- Hospitalisation for UTI, sepsis, or acute kidney injury (AKI) within 14 days following the incident UTI ascertained from ICD-10 codes recorded in linked hospital admission data for the first episode of a hospital admission, i.e., the episode most likely responsible for the admission.
- Death within 28 days following the incident UTI using linked death registration data.

Statistical analyses

The authors used primary care demographic and clinical codes to describe baseline characteristics for patients by exposure status.

To assess the impact of eGFR, the authors compared rates of each outcome in those with an eGFR ≥60 mL/min/1.73 m^2 to those in each category related to an eGFR <60 mL/min/1.73 m_2, and used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

Potential confounders of the association between renal impairment and outcome, including: age; Index of Multiple Deprivation score quintile; Charlson comorbidity score; the presence or absence of a record indicating diabetes, dementia, coronary heart disease, stroke, cancer, and heart failure; and polypharmacy were adjusted for. The authors inferred the presence of polypharmacy if the patient's record showed repeated monthly prescribing of ≥5 medications in the year prior to the incident UTI.

To assess the impact of empirical trimethoprim versus nitrofurantoin prescribing, a range of demographic and clinical variables were used to match patients on their propensity to receive a trimethoprim prescription. These included the confounders listed above and presence or absence of a record indicating urinary incontinence or long-term catheterisation, and long-term prescribing of angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, or potassium-sparing diuretics.

The authors used nearest neighbour matching with no replacement and matched each patient with a nitrofurantoin prescription to three patients with trimethoprim prescriptions. The authors used mixed effects logistic regression to account for clustering by general practice and calculated ORs and 95% CIs for each outcome.

3.2.1.2 Results

From a cohort of 795,484 patients aged 65 and over, we identified 123,607 with an incident UTI empirically treated with a relevant antibiotic. 116,945 (95%) of the 123,607 patients had a creatinine measurement recorded in the 24 months prior to the incident UTI.

In this final cohort (n=116,945), 32,428 (28%) were male. The median age at the time of incident UTI was 76 years (IQR 70-83). Almost one third of creatinine measurements were in the 90 days prior to the incident UTI. Median duration between most recent creatinine and UTI was 169 days (IQR 65-285).

Using the MDRD study equation, 76,112 (65.1%) of patients were assigned an eGFR ≥60, 26,970 (23.1%) an eGFR of 45-59, 10,854 (9.3%) an eGFR of 30-44, 2,667 (2.3%) an eGFR of 15-29, and 342 (0.3%) an eGFR of <15.

Baseline characteristics showed that patients with lower eGFRs had a relatively greater number of comorbidities and comprised greater proportions of patients with polypharmacy. Trimethoprim was the most commonly prescribed empirical antibiotic across all eGFR groups. Nitrofurantoin was the second most common except in patients with an eGFR <15 mL/minute/1.73 m^2.

Table 1. Baseline characteristics of included patients according to eGFR category.

Characteristics	eGFR ≥60	eGFR 45–59	eGFR 30–44	eGFR 15–29	eGFR <15
N	76,112 (65.1)	26,970 (23.1)	10,854 (9.3)	2,667 (2.3)	342 (0.3)
Men	21,816 (28.7)	6,674 (24.7)	2,894 (26.7)	880 (33.0)	164 (48.0)
Mean (SD) age	75.2 (7.9)	79.1 (8.3)	82.5 (8.0)	83.2 (8.0)	79 (8.2)
Prescribed antibiotic					
Amoxicillin	3,370 (4.4)	1,367 (5.1)	680 (6.3)	289 (10.8)	45 (13.2)
Cefalexin	4,168 (5.5)	1,749 (6.5)	917 (8.4)	319 (12.0)	47 (13.7)
Ciprofloxacin	2,344 (3.1)	811 (3.0)	388 (3.6)	148 (5.5)	26 (7.6)
Co-amoxiclav	3,170 (4.2)	1,227 (4.5)	613 (5.6)	208 (7.8)	44 (12.9)
Nitrofurantoin	16,719 (22.0)	5,237 (19.4)	1,815 (16.7)	391 (14.7)	41 (12.0)
Trimethoprim	46,341 (60.9)	16,579 (61.5)	6,441 (59.3)	1,312 (49.2)	139 (40.6)
Index of multiple deprivation decile					
1 or 2 (least deprived)	19,939 (26.2)	6,401 (23.7)	2,292 (21.1)	560 (21.0)	65 (19.0)
3 or 4	18,413 (24.2)	6,524 (24.2)	2,526 (23.3)	619 (23.2)	77 (22.5)
5 or 6	16,606 (21.8)	5,859 (21.7)	2,443 (22.5)	615 (23.1)	85 (24.9)
7 or 8	12,283 (16.1)	4,626 (17.2)	1,918 (17.7)	477 (17.9)	45 (13.2)
9 or 10 (most deprived)	8,871 (11.7)	3,560 (13.2)	1,675 (15.4)	396 (14.8)	70 (20.5)
Housebound	2,261 (3.0)	1,201 (4.5)	866 (8.0)	267 (10.0)	34 (9.9)
Respiratory disease	15,853 (20.8)	5,521 (20.5)	2,208 (20.3)	538 (20.2)	46 (13.5)
Cardiac failure	2,187 (2.9)	1,733 (6.4)	1,367 (12.6)	499 (18.7)	56 (16.4)
Dementia	3,724 (4.9)	2,024 (7.5)	1,129 (10.4)	265 (9.9)	21 (6.1)
Peripheral vascular disease	2,903 (3.8)	1,502 (5.6)	953 (8.8)	319 (12.0)	43 (12.6)
Rheumatoid arthritis	2,140 (2.8)	803 (3.0)	339 (3.1)	97 (3.6)	9 (2.6)
Cancer	11,291 (14.8)	4,211 (15.6)	1,891 (17.4)	498 (18.7)	82 (24.0)
Stroke	6,714 (8.8)	3,123 (11.6)	1,695 (15.6)	454 (17.0)	67 (19.6)
Diabetes	11,956 (15.7)	5,103 (18.9)	2,863 (26.4)	961 (36.0)	112 (32.7)
Liver disease	445 (0.6)	165 (0.6)	69 (0.6)	11 (0.4)	3 (0.9)
Ischaemic heart disease	11,611 (15.3)	5,814 (21.6)	3,118 (28.7)	878 (32.9)	114 (33.3)
Urinary catheter	2,360 (3.1)	854 (3.2)	504 (4.6)	193 (7.2)	39 (11.4)
Urinary incontinence	10,966 (14.4)	4,089 (15.2)	1,702 (15.7)	398 (14.9)	41 (12.0)
Polypharmacy	24,478 (32.2)	11,419 (42.3)	6,371 (58.7)	1,797 (67.4)	237 (69.3)
Potassium-sparing diuretic	1,470 (1.9)	946 (3.5)	732 (6.7)	158 (5.9)	4 (1.2)
Angiotensin-converting enzyme inhibitor	16,430 (21.6)	7,586 (28.1)	3,446 (31.7)	718 (26.9)	46 (13.5)
Angiotensin-II receptor antagonist	8,195 (10.8)	3,933 (14.6)	1,885 (17.4)	453 (17.0)	42 (12.3)
Charlson score					
0	30,663 (40.3)	6,131 (22.7)	879 (8.1)	104 (3.9)	6 (1.8)
1	18,770 (24.7)	4,100 (15.2)	824 (7.6)	116 (4.3)	12 (3.5)
2	12,973 (17.0)	6,309 (23.4)	2,621 (24.1)	504 (18.9)	81 (23.7)
3	7,394 (9.7)	4,666 (17.3)	2,424 (22.3)	577 (21.6)	64 (18.7)
4	3,219 (4.2)	2,725 (10.1)	1,728 (15.9)	481 (18.0)	66 (19.3)
5	1,636 (2.1)	1,661 (6.2)	1,148 (10.6)	401 (15.0)	45 (13.2)
≥6	1,457 (1.9)	1,378 (5.1)	1,230 (11.3)	484 (18.1)	68 (19.9)

Numbers are values (%) unless otherwise stated.

Outcomes according to calculated eGFR

There were 7,203 reconsultations with urinary symptoms resulting in another antibiotic prescription within 14 days of the incident UTIs, equating to about 6% of the cohort. The odds of reconsulting and receiving another antibiotic prescription were no different between those with an eGFR ≥60 mL/min/1.73 m^2 and those with eGFRs <60mL/min/1.73 m^2.

There were 1,991 hospitalisations for UTI (1.7% of the cohort), 176 for sepsis (0.2% of the cohort), and 865 for AKI (0.7% of the cohort) within 14 days of the incident UTIs. Compared to those with an eGFR ≥60 mL/min/1.73 m^2, odds of hospitalisation for UTI increased in those with eGFRs of 45-59

(adjusted OR 1.14, 95% CI 1.01-1.28), 30-44 (adjusted OR 1.25, 95% CI 1.08-1.44), 15-29 (adjusted OR 1.76, 95% CI 1.43-2.16), and <15 (adjusted OR 1.68, 95% CI 1.01-2.82).

Odds of hospitalisation for sepsis were no different in those with an eGFR of 45-59 but were significantly higher in those with eGFRs of 30-44 (adjusted OR 1.70, 95%CI 1.06-2.72), 15-29 (adjusted OR 2.72, 95% CI 1.50-4.94), and <15 (adjusted OR 4.24, 95%CI 1.48-11.23).

The risk of hospitalisation for AKI increased in a graded manner relative to renal function, with adjusted ORs of 1.57 (95% CI 1.29-1.91), 3.21 (95% CI 2.61-3.94), 6.70 (95% CI 5.24-8.55), and 4.53 (95% CI 2.52-8.17) for eGFRs of 45-59, 30-44, 15-29, and <15mL/min/1.73 m^2, respectively.

There were 1,162 deaths in the 28 days following the incident UTIs, equating to about 1% of the cohort. Compared to those with an eGFR ≥60 mL/min/1.73 m^2, the odds of death were no different in those with an eGFR ≥30 mL/min/1.73 m^2, 63% higher in those with an eGFR of 15-29 (adjusted OR 1.63, 95% CI 1.27-2.10), and over 2-fold higher in those with an eGFR <15 (adjusted OR 2.37, 95% CI 1.44-3.89).

Table 2. Adjusted ORs and 95% CIs for each outcome by eGFR category.

Reconsultation and re-prescription within 14 days	Number of UTIs	Number (%) of events	Crude OR	Adjusted* OR (95% CI)	*p*-value
eGFR ≥60	76,112	4,852 (6.4)	1	1	
eGFR 45–59	26,970	1,563 (5.8)	0.90	0.97 (0.91–1.03)	0.328
eGFR 30–44	10,854	626 (5.8)	0.90	1.03 (0.94–1.14)	0.511
eGFR 15–29	2,667	148 (5.5)	0.86	1.02 (0.86–1.22)	0.804
eGFR <15	342	14 (4.1)	0.63	0.72 (0.42–1.23)	0.224
Hospitalised for UTI within 14 days					
eGFR ≥60	76,112	1,003 (1.3)	1	1	
eGFR 45–59	26,970	526 (2.0)	1.49	1.14 (1.01–1.28)	0.028
eGFR 30–44	10,854	317 (2.9)	2.25	1.25 (1.08–1.44)	0.003
eGFR 15–29	2,667	129 (4.8)	3.81	1.76 (1.43–2.16)	<0.001
eGFR <15	342	16 (4.7)	3.68	1.68 (1.01–2.82)	<0.001
Hospitalised for sepsis within 14 days					
eGFR ≥60	76,112	77 (0.1)	1	1	
eGFR 45–59	26,970	46 (0.2)	1.69	1.36 (0.92–2.01)	0.119
eGFR 30–44	10,854	32 (0.3)	2.92	1.70 (1.06–2.72)	0.027
eGFR 15–29	2,667	17 (0.6)	6.33	2.72 (1.50–4.94)	<0.001
eGFR <15	342	4 (1.2)	11.69	4.24 (1.48–11.23)	0.007
Hospitalised for AKI within 14 days					
eGFR ≥60	76,112	280 (0.4)	1	1	
eGFR 45–59	26,970	204 (0.8)	2.06	1.57 (1.29–1.91)	<0.001
eGFR 30–44	10,854	231 (2.1)	5.89	3.21 (2.61–3.94)	<0.001
eGFR 15–29	2,667	137 (5.1)	14.67	6.70 (5.24–8.55)	<0.001
eGFR <15	342	13 (3.8)	10.70	4.53 (2.52–8.17)	<0.001
Death within 28 days					
eGFR ≥60	76,112	588 (0.8)	1	1	
eGFR 45–59	26,970	285 (1.1)	1.37	0.92 (0.79–1.07)	0.275
eGFR 30–44	10,854	201 (1.9)	2.42	1.05 (0.87–1.26)	0.598
eGFR 15–29	2,667	99 (3.7)	4.95	1.63 (1.27–2.10)	<0.001
eGFR <15	342	19 (5.6)	7.56	2.37 (1.44–3.89)	<0.001

*ORs adjusted for age, gender, Index of Multiple Deprivation score quintile, Charlson comorbidity score, being housebound, respiratory disease, peripheral vascular disease, liver disease, rheumatoid arthritis, diabetes, dementia, coronary heart disease, stroke, cancer, heart failure, polypharmacy, long-term prescribing of angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, or potassium-sparing diuretics, urinary catheter, urinary incontinence, and choice and duration of antibiotic therapy.

Abbreviations: AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; UTI, urinary tract infection.

Trimethoprim versus nitrofurantoin in those with an eGFR <60mL/min/1.73m^2

Of the 40,833 patients with an eGFR <60 mL/minute/1.73 m_2, 24,471 (60%) were prescribed trimethoprim and 7,484 (18%) were prescribed nitrofurantoin.

The authors matched 20,948 patients with an eGFR of 45-60 (15,711 prescribed trimethoprim, 5,237 prescribed nitrofurantoin), 7,260 with an eGFR of 30-44 (5,445 prescribed trimethoprim, 1,815 prescribed nitrofurantoin), and 1,728 with an eGFR <30 (1,296 prescribed trimethoprim, 432 prescribed nitrofurantoin). Inspection of jitter plots and histograms suggested matching had

improved balance of covariates across trimethoprim versus nitrofurantoin groups. Standardised mean differences were all less than 0.1.

Empirical nitrofurantoin prescribing was associated with lower odds of hospitalisation for AKI across all eGFR groups compared to trimethoprim (eGFR 45-59: OR 0.62, 95% CI 0.40-0.94; eGFR 30-44: OR 0.47, 95% CI 0.30-0.73; eGFR <30: OR 0.45, 95% CI 0.25-0.81) Nitrofurantoin was also associated with lower odds of reconsultation and re-prescription in patients with eGFRs of 45-59 (OR 0.74, 95% CI 0.61-0.91) and lower odds of death in patients with eGFRs of 30-44 (OR 0.61, 95% CI 0.39-0.95). There were no other statistically significant differences between empirical trimethoprim versus nitrofurantoin prescribing. Importantly, the authors did not detect any increase in odds of adverse outcomes in patients prescribed nitrofurantoin.

Table 4. ORs and 95% CIs for each outcome in propensity-score* matched trimethoprim versus nitrofurantoin groups, across three eGFR categories.

eGFR 45–59	**Trimethoprim group, *n* = 15,711**	**Nitrofurantoin group, *n* = 5,237**	**OR (95% CI)**	***p*-value**
	Number (%) of events	**Number (%) of events**		
Death within 28 days	159 (1.0)	50 (1.0)	0.94 (0.69–1.30)	0.718
Reconsultation and re-prescription within 14 days	942 (6.0)	290 (5.5)	0.74 (0.61–0.91)	0.004
Hospitalised for UTI within 14 days	288 (1.8)	105 (2.0)	1.09 (0.74–1.61)	0.648
Hospitalised for sepsis within 14 days	25 (0.2)	6 (0.72)	0.72 (0.30–1.76)	0.470
Hospitalised for AKI within 14 days	126 (0.8)	26 (0.5)	0.62 (0.40–0.94)	0.025
eGFR 30–44	**Trimethoprim group, *n* = 5,445**	**Nitrofurantoin group, *n* = 1,815**		
	Number (%) of events	**Number (%) of events**	**OR (95% CI)**	***p*-value**
Death within 28 days	113 (2.1)	23 (1.3)	0.61 (0.39–0.95)	<0.001
Reconsultation and re-prescription within 14 days	318 (5.8)	117 (6.4)	0.98 (0.71–1.33)	0.874
Hospitalised for UTI within 14 days	168 (3.1)	57 (3.1)	0.80 (0.44–1.47)	0.482
Hospitalised for sepsis within 14 days	14 (0.3)	2 (0.1)	0.43 (0.10–1.88)	0.262
Hospitalised for AKI within 14 days	146 (2.7)	23 (1.3)	0.47 (0.30–0.73)	<0.001
eGFR < 30	**Trimethoprim group, *n* = 1,296**	**Nitrofurantoin group, *n* = 432**		
	Number (%) of events	**Number (%) of events**	**OR (95% CI)**	***p*-value**
Death within 28 days	49 (3.8)	18 (4.2)	1.11 (0.64–1.93)	0.713
Reconsultation and re-prescription within 14 days	74 (5.7)	29 (6.7)	1.19 (0.76–1.85)	0.446
Hospitalised for UTI within 14 days	73 (5.6)	23 (5.3)	0.94 (0.58–1.53)	0.808
Hospitalised for sepsis within 14 days	8 (0.6)	2 (0.5)	0.75 (0.16–3.54)	0.715
Hospitalised for AKI within 14 days	84 (6.5)	13 (3.0)	0.45 (0.25–0.81)	0.008

*The following baseline variables were used in the propensity-score model: age, gender, Index of Multiple Deprivation score quintile, Charlson comorbidity score, being housebound, the presence or absence of respiratory disease, peripheral vascular disease, liver disease, rheumatoid arthritis, diabetes, dementia, coronary heart disease, stroke, cancer, heart failure, urinary catheter, urinary incontinence, polypharmacy, long-term prescribing of angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, or potassium-sparing diuretics.

Abbreviations: AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio; UTI, urinary tract infection.

3.2.1.3 Discussion

The authors consider that their results show that compared to an eGFR of >60 mL/min/1.73 m^2, older patients with an eGFR of <60 mL/min/1.73 m^2 who were empirically treated for suspected UTI in primary care had greater odds of hospitalisation for UTI and AKI, those with an eGFR <45 had greater odds of hospitalisation for sepsis, and those with an eGFR <30 had greater odds of death. The magnitude of each association generally increased relative to the severity of the renal impairment.

Ccompared to trimethoprim, nitrofurantoin was associated with reduced odds of hospitalisation for AKI across all eGFR groups and was not associated with an increased risk of any adverse event evaluated in this study.

Nitrofurantoin, compared with trimethoprim, was associated with lower odds of reconsultation and re-prescription in patients with eGFRs of 45-59. This could be explained by recent data showing that 34% of community acquired *Escherichia* coli UTIs in England are resistant to trimethoprim, compared to only 2.7% resistant to nitrofurantoin. A statistically significant difference between reconsultation and re-prescription rates in people with eGFRs <45 was not identified. This could be due to less statistical power, as nitrofurantoin use was less common in these patients because of the advice to use with care in patients with eGFRs of 30-44 and to avoid in eGFRs <30. It may also be due to the possibility that nitrofurantoin efficacy was reduced in those with lower eGFRs but was offset by the

high rates of trimethoprim resistance and thus resulted in apparent similar rates of reconsultation and re-prescription.

Strengths of this study:

The authors identified the following as strengths:

- the study used data from a general practice database that is broadly representative of the UK population, increasing the generalisability of our findings.
- This is the largest cohort study to investigate the impact of eGFR on infection-related outcomes.
- Cohort entry was dependent on presentation and empirical treatment of UTI in primary care, and thus reduced indication bias.
- The study adjusted for the presence/absence of more comorbidities than previous studies, increasing the likelihood of an independent association between eGFR and adverse outcomes.
- This is the first study to investigate trimethoprim versus nitrofurantoin prescribing in renal impairment, using clinically relevant eGFR groups analogous to stages of chronic kidney disease and without excluding men.
- The study reduced indication bias by matching patients on their propensity to receive trimethoprim, and achieving adequate balance of covariates across the two groups.

Limitations of this study:

The authors identified the following as limitations:

- The study attempted to capture patients presenting with UTI but had no microbiological data to support this. However, whilst a limitation, this is also more representative of clinical practice.
- investigatation of pulmonary/hepatic toxicity related to nitrofurantoin use was not possible because of the lack of reliable codes, and differential use of these codes by clinicians.
- Creatinine measurement from the 24 months prior to the UTI to estimate an eGFR, may not fully represent patients' current renal function.
- Finally, despite the design, differential coding, indication bias, and residual confounding may still have affected the findings.

3.2.1.4 Conclusion

The authors state that their findings show that older patients with renal impairment presenting to primary care with a UTI are at greater risk of adverse outcomes independent of other comorbidities and of prescribed empirical antibiotic treatment.

Despite documented concerns, they found no increased risk of adverse outcomes in patients with an eGFR <60 mL/min/1.73 m^2 prescribed nitrofurantoin compared to patients prescribed trimethoprim. The authors support its wider use in selected patients with moderate-severe renal impairment.

3.2.2 Muller et al (2017) - Nitrofurantoin's efficacy and safety as prophylaxis for urinary tract infections: a systematic review of the literature and meta-analysis of controlled trials (Annex 4)

This was a systematic review of all controlled trials in humans assessing nitrofurantoin for UTI prophylaxis published from 1946 to 2015. The authors also reviewed population-level cohort studies evaluating nitrofurantoin's toxicity. Meta-analyses assessing efficacy and adverse events were conducted on controlled trials.

Twenty-six controlled trials including 3052 patients fulfilled entry criteria for the systematic review and meta-analysis on efficacy and toxicity, and 16 population-level cohort studies were identified for review of toxicity. Overall quality was poor, with all studies at increased risk for various biases.

The authors state that their systematic search of the literature did not yield any robust information on nitrofurantoin's efficacy and toxicity in special populations, such as the elderly and those with renal insufficiency.

3.2.3 Cunha et al (2017) - Nitrofurantoin safety and effectiveness in treating acute uncomplicated cystits (AUC) in hospitalized adults with renal insufficiency: antibiotic stewardship implications (Annex 5)

3.2.3.1 Methods

This was a retrospective chart review over an 18 month period of hospitalised adults with acute uncomplicated cystitis (AUC) and renal insufficiency (CrCl = 30-60mL/min). The study aimed to determine the safety and efficacy of nitrofurantoin in this group.

Creatinine clearances were calculated on the basis of age, sex and weight.

All patients received nitrofurantoin 100 mg per oral (PO) q12h (every 12 hours) for 5-7 days. Repeat urinalysis and urine culture was done on the final day of therapy. Urinary isolates susceptibility testing was done by micro broth dilution (MBD).

Exclusion criteria

- Patients with complicated urinary tract infections (UTIs)
- Patients with inadequate clinical data or repeat urinalysis and urine culture.

Study endpoints

- Clinical success was defined as a marked decrease in intensity of pyuria (pus in the urine) and elimination of the uropathogen after 5–7 days.
- Clinical failure was defined as little/no decrease in intensity of pyuria (pus in the urine) and no decrease in urine colony counts.

Comment: The date range and location of this retrospective study are not mentioned. The primary author (B.A Cunha) was affiliated with the Infectious Disease Division, Winthrop-University Hospital, New York. One co-author (C.B. Cunha) was affiliated with Rhode Island Hospital and the Miriam Hospital, Rhode Island.

The exact equation used to calculate patient renal function was not stated.

3.2.3.2 Results

There were 26 evaluable patients, three quarters were female and ranged in age from 54 to 90 years old.

Nitrofurantoin was highly effective in eradicating bacteriuria due to susceptible organisms in hospitalized adults with AUC and a CrCl < 60 ml/min. An early decrease in pyuria intensity (during the first three days of therapy) was an important predicator of subsequent negative urine cultures.

Of the 8 (31%) treatment failures, most were due to inappropriate spectrum, i.e., intrinsically resistant uropathogens e.g. *Proteus sp.* (5 cases), or suboptimal urinary pH (alkaline) (1 case). There were only two nitrofurantoin failures due to renal insufficiency in patients with CrCl < 30 ml/min. There were no adverse nitrofurantoin events.

Table 2: Summary of results of nitrofurantoin treatment of acute uncomplicated cystitis (AUC) in hospitalized adults with renal insufficiency (CrCl <60mL/min)

Number of evaluable patients (N = 26)	Creatinin clearance (CrCl)	Outcome	Uropathogens					
			E. coli	*Klebsiella pneumoniae*	*Enterobacter sp.*	*Proteus sp.*	GBS	VSE/VRE
			C/F	C/F	C/F	C/F	C/F	C/F
Evaluable, n = 4	CrCl = 50-60 ml/min	Cured = 3/4 Failed = 1/4	3/0	None	0/1[b]	None	None	None
Evaluable, n = 11	CrCl = 40-50 ml/min	Cured = 9/11 Failed = 2/11	6/0	0/1b[b]	None	0/1[c]	1/0	2/0
Evaluable, n = 9	CrCl = 30-40 ml/min	Cured = 4/9 Failed = 5/9	4/1	None	0	0/2[c]	0/2[c]	None
Evaluable, n = 2	CrCl < 30 ml/min	Cured = 0/2 Failed = 2/2	0/2	None	None	None	None	None

GBS Group B streptococci, *VSE* vancomycin susceptible enterococci, *VRE* vancomycin resistant enterococci, *C* cured, *F* failed

[a] 5-7 days of therapy of nitrofurantoin with 100 mg (PO) q12h

[b] Suboptimal urinary pH (alkaline urine) for nitrofurantoin

[c] *Proteus sp.*

3.2.3.3 Conclusion

The authors state: In summary, in our recent 18-month experience, in 26 evaluable hospitalized adults with AUC, nitrofurantoin was highly effective against susceptible uropathogens if the CrCl was >30 ml/min, particularly with an acid urinary pH.

With nitrofurantoin, the next most important factor in optimizing effectiveness after high urinary concentrations is urinary pH dependent antimicrobial activity. Urinary pH may increase or decrease nitrofurantoin's activity. Nitrofurantoin effectiveness is optimal if the CrCl > 30 ml/min with an acid (pH < 5.5) urinary pH. Nitrofurantoin may be used safely and effectively with renal insufficiency with a CrCl > 30 ml/min.

Comment: The authors suggest a CrCl cut-off point of 30mL/min, based on data from 26 patients.

3.2.4 Santos et al (2016) – Evaluation of the Risk of Nitrofurantoin Lung Injury and Its Efficacy in Diminished Kidney Function in Older Adults in a Large Integrated Healthcare System: A Matched Cohort Study (Annex 6)

3.2.4.1 Methods

This retrospective, matched-cohort study analysed data from electronic medical records at Kaiser Permanente Southern California, an integrated healthcare system, from January 1, 2007, through to December 31, 2013.

The objectives of the study were to determine the risk to older adults of lung injury associated with treatment of cystitis using nitrofurantoin and the risk of treatment failure in the presence of diminished creatinine clearance (CrCl).

Inclusion Criteria

- A diagnosis of cystitis between 2007 and 2012 according to International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes
- aged 65 and over
- at least 30 days of continuous health plan enrolment before cystitis diagnosis
- and exposure to an antibiotic that the Infectious Diseases Society of America (IDSA) recommends for treatment of cystitis

Exclusion criteria

- aged younger than 65
- diagnosis of another lung disease,
- use of other medications associated with pulmonary toxicity

Examining lung injury

To examine the association between nitrofurantoin and lung injury, individuals with new lung disease diagnosed after exposure to nitrofurantoin were identified according to ICD-9 codes.

Because the latent period from drug exposure to lung injury is highly variable, ranging from minutes to years, any diagnosis after exposure was considered, and lung injury was defined as any diagnosis after the dispense date of nitrofurantoin. Cases' nitrofurantoin dispense date was used as the index date for matched controls. Lung diseases caused by other known exposures were excluded and individuals with these diagnoses were not included in the analysis.

Nitrofurantoin users were matched in a 1:3 ratio with control subjects who, during the same time period, were exposed to other antibiotics used to treat cystitis. This was done using simple ("greedy") nearest neighbour matching according to age (± 5 years), sex, race, ethnicity, and initial prescription date as the index date (± 90 days)

Acute vs chronic nitrofurantoin treatment

Acute nitrofurantoin treatment was defined as less than 14 days of prescribed antibiotic treatment from the index date and chronic treatment as 14 days of prescribed antibiotic treatment or more from the index date.

Follow-up duration

Length of follow-up was calculated from study entry (diagnosis date of cystitis) to study end (December 31, 2013), death, lung injury diagnosis, or end of membership.

Statistical Analysis

Categorical variables were assessed using the chi-square test and continuous variables using the parametric Student t-test or nonparametric Kruskal–Wallis test, as appropriate.

Conditional logistic regression was used to estimate crude and multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between lung injury and use of nitrofurantoin. The adjusted analyses accounted for confounding by education status, neighbourhood household income, chronic treatment status, and Charlson Comorbidity Index using the Quan adaptation. Because incident cases of nitrofurantoin exposure were used that were matched with controls, were matched on time, and were from a dynamic population, ORs were taken as estimating risk ratios.

Multivariable logistic regression in only the nitrofurantoin-exposed group was used to assess chronic treatment status as the exposure of interest. Because these data were not matched, confounding by age at diagnosis, sex, and race and ethnicity were also adjusted for.

Nitrofurantoin treatment failure rate according to creatinine clearance (CrCl)

Last, the failure rate of nitrofurantoin for treatment was studied according to CrCl category by assessing the overall association between CrCl categories (≤30, 30–60, ≥60 mL/min) and each of the demographic characteristics and treatment failure status.

CrCl was calculated using the Cockcroft-Gault equation using the serum creatinine level (and participant weight) closest to the time of the initial nitrofurantoin prescription.

Treatment failure was defined as dispensing of another antibiotic for cystitis within 21 days after the index date.

Finally, a post hoc chi-square test, Student t-test, or Wilcoxon rank test was performed, as appropriate, to assess differences within categories of CrCl.

Study population

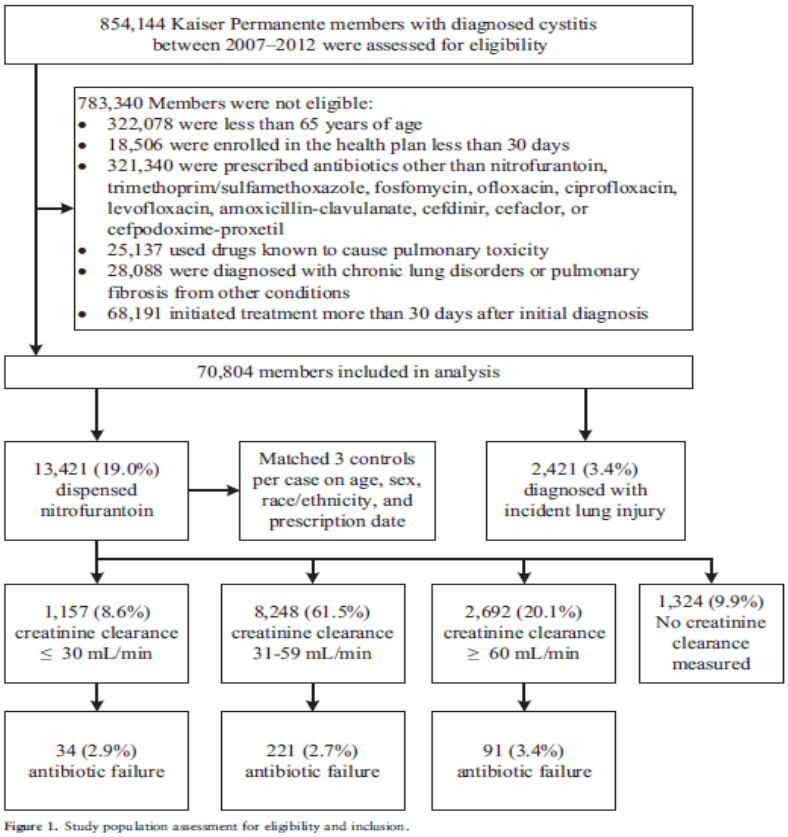

Figure 1. Study population assessment for eligibility and inclusion.

3.2.4.2 Results

Baseline characteristics of the matched cohort are shown in Table 1 below. The sample size was 45,521 participants, with 13,421 given nitrofurantoin (cases) and 32,100 matched individuals given other antibiotics (controls). There were more women than men, and most were non-Hispanic white or Hispanic. Both groups were more commonly given antibiotics as an acute regimen. Four hundred and ninety-one lung injury outcomes were observed among cases and 1,286 among matched controls.

Crude and multivariable-adjusted conditional logistic regression risk ratios for the matched cohort were estimated. The unadjusted risk of lung injury in participants taking nitrofurantoin was not statistically significantly different from that of those not taking nitrofurantoin (crude risk ratio (RR) = 0.90, 95% CI = 0.81–1.01). Adjustment for chronic treatment, neighbourhood education, and neighbourhood median household income did not change the difference (adjusted RR (aRR) = 0.90, 95% CI = 0.80–1.00). Age, sex, race and ethnicity, and time of treatment were controlled for by matching and were therefore not included in the model.

The risk of lung injury in participants undergoing chronic antibiotic treatment was not statistically significantly different from that of those undergoing acute antibiotic treatment (RR = 1.26, 95% CI = 0.90–1.76; aRR = 1.30, 95% CI = 0.93–1.81).

With an overall sample size of 45,521, the logistic regression two-sided test of the observed exposure OR with a type I error rate of 5% had 98% power to detect a change in OR of 10%.

Table 1. Characteristics of Health Plan Members Given Nitrofurantoin (Cases) and Corresponding Controls Taking Other Antibiotics for Urinary Tract Infection: 2007–2013

Characteristic	Controls, n = 32,100	Cases, n = 13,421	Total, N = 45,521	Unadjusted Risk Ratio (95% Confidence Interval)
Lung injury, n (%)				
No	30,814 (96.0)	12,930 (96.3)	43,744 (96.1)	Reference
Yes	1,286 (4.0)	491 (3.7)	1,777 (3.9)	0.91 (0.82–1.01)
Age at diagnosis				
Mean ± SD	74.7 ± 7.2	73.7 ± 6.9	74.4 ± 7.1	N/A
Median	73.5	72.0	73.0	
Interquartile range	69.0–80.0	68.0–78.0	68.0–79.0	
Range	65.0–101.0	65.0–100.0	65.0–101.0	
Sex, n (%)				
Female	28,817 (89.8)	12,325 (91.8)	41,142 (90.4)	N/A
Male	3,283 (10.2)	1,096 (8.2)	4,379 (9.6)	
Race and ethnicity, n (%)				
Non-Hispanic white	18,682 (58.2)	7,825 (58.3)	26,507 (58.2)	N/A
Non-Hispanic black	3,152 (9.8)	1,120 (8.3)	4,272 (9.4)	
Hispanic	7,137 (22.2)	3,210 (23.9)	10,347 (22.7)	
Native American, Alaskan	16 (0)	10 (0.1)	26 (0.1)	
Asian, Pacific Islander	2,129 (6.6)	822 (6.1)	2,951 (6.5)	
Other	984 (3.1)	434 (3.2)	1,418 (3.1)	
Vital status, n (%)				
Alive	25,665 (80)	11,429 (85.2)	37,094 (81.5)	Reference
Died	6,435 (20)	1,992 (14.8)	8,427 (18.5)	0.70 (0.65–0.74)
Days supply				
Mean ± SD	7.0 ± 3.4	8.7 ± 11.3	7.5 ± 6.8	1.05 (1.04–1.05)
Median	7.0	7.0	7.0	
Interquartile range	5.0–10.0	7.0–7.0	5.0–9.0	
Range	0.0–100.0	0.0–100.0	0.0–100.0	
Treatment (days), n (%)				
Acute (< 14)	31,381 (97.8)	12,890 (96.1)	44,271 (97.3)	Reference
Chronic (≥14)	718 (2.2)	530 (3.9)	1,248 (2.7)	1.90 (1.69–2.14)
1-year Charlson Comorbidity Index, n (%)				
0	12,471 (38.9)	6,138 (45.7)	18,609 (40.9)	Reference
1–2	13,252 (41.3)	5,306 (39.5)	18,558 (40.8)	0.94 (0.91–0.98)
≥3	6,376 (19.9)	1,977 (14.7)	8,353 (18.4)	0.73 (0.69–0.77)
Length of follow-up, years				
Mean ± SD	3.0 ± 2.3	4.3 ± 2.3	4.0 ± 2.3	1.06 (1.05–1.08)
Median	3.9	4.4	4.1	
Interquartile range	2.0–5.9	2.7–6.2	2.2–6.0	
Range	0.0–8.0	0.0–8.0	0.0–8.0	

N/A = applicable; SD = standard deviation.

The baseline characteristics of the study population used for the second aim of the study are presented in Table 2 below, according to acute or chronic nitrofurantoin exposure status. There was a higher proportion of men in the chronic group than in the acute group, and the chronic group was slightly older.

Table 2. Characteristics of 13,421 Health Plan Members Given Nitrofurantoin for Urinary Tract Infection: 2007–2013

Characteristic	Acute (< 14 Days), n = 12,890	Chronic (≥14 Days, n = 530	Total, N = 13,421	*P*-Value
Lung injury, n (%)				
No	12,431 (96.4)	498 (94.0)	12,930 (96.3)	.003
Yes	459 (3.6)	32 (6.0)	491 (3.7)	
Days supply				
Mean ± SD	7.0 ± 1.6	50.7 ± 37.0	8.7 ± 11.3	<.001
Median	7	30	7	
Interquartile range	7.0, 7.0	14.0, 100.0	7.0, 7.0	
Range	1.0–12.0	14.0–100.0	0.0–100.0	
Age at diagnosis				
Mean ± SD	73.7 ± 6.9	74.4 ± 7.2	73.7 ± 6.9	.03
Median	72	74	72	
Interquartile range	68.0–78.0	68.0–80.0	68.0–78.0	
Range	65.0–100.0	65.0–99.0	65.0–100.0	
Sex, n (%)				
Female	11,911 (92.4)	413 (77.9)	12,325 (91.8)	<.001
Male	979 (7.6)	117 (22.1)	1,096 (8.2)	
Race and ethnicity, n (%)				
Non-Hispanic white	7,441 (57.7)	384 (72.5)	7,825 (58.3)	<.001
Non-Hispanic black	1,100 (8.5)	20 (3.8)	1,120 (8.3)	
Hispanic	3,125 (24.2)	84 (15.8)	3,210 (23.9)	
Native American, Alaskan	10 (0.1)	0 (0)	10 (0.1)	
Asian, Pacific Islander	792 (6.1)	30 (5.7)	822 (6.1)	
Other	422 (3.3)	12 (2.3)	434 (3.2)	
Vital status, n (%)				
Alive	11,021 (85.5)	407 (76.8)	11,429 (85.2)	<.001
Died	1,869 (14.5)	123 (23.2)	1,992 (14.8)	
1-year Charlson Comorbidity Index, n (%)				
0	5,912 (45.9)	225 (42.5)	6,138 (45.7)	.007
1–2	5,104 (39.6)	202 (38.1)	5,306 (39.5)	
≥3	1,874 (14.5)	103 (19.4)	1,977 (14.7)	
Length of follow-up, years				
Mean ± SD	4.3 ± 2.3	4.2 ± 2.6	4.3 ± 2.3	.80
Median	4.4	4.2	4.4	
Interquartile range	2.7–6.2	1.9–6.7	2.7–6.2	
Range	0.0–8.0	0.0–8.0	0.0–8.0	

SD = standard deviation.

Table 3. Risk of Lung Injury in the 13,421 Participants Given Nitrofurantoin: 2007–2013

Characteristic	Crude	Multivariable Adjusted
	Risk Ratio (95% Confidence Interval)	
Age at diagnosis (reference 65–74)		
75–84	1.70 (1.39–2.07)	1.43 (1.17–1.75)
≥85	2.32 (1.74–3.07)	1.81 (1.37–2.40)
Male	1.31 (0.95–1.78)	0.96 (0.71–1.31)
Race and ethnicity (reference non-Hispanic white)		
Non-Hispanic black	0.70 (0.49–0.99)	0.68 (0.47–0.97)
Hispanic	0.57 (0.44–0.72)	0.60 (0.47–0.77)
Native American, Alaskan	NE	NE
Asian, Pacific Islander	0.51 (0.32–0.82)	0.55 (0.34–0.87)
Other	0.57 (0.31–1.04)	0.68 (0.37–1.26)
≥14 days treatment	1.72 (1.15–2.50)	1.50 (1.03–2.19)
1-year Charlson Comorbidity Index (reference 0)		
1–2	2.09 (1.67–2.61)	2.00 (1.61–2.49)
≥3	3.10 (2.39–4.00)	2.85 (2.20–3.69)

NE = not estimable.

Table 3 above presents the crude and multivariable aRRs for lung injury in this population. There was a significantly greater risk of lung injury with chronic than with acute nitrofurantoin exposure (RR = 1.53, 95% CI = 1.04–2.24). Participants aged 75–84 were at higher risk of lung injury than those younger than 65 (RR = 1.56, 95% CI = 1.28–1.91), and those aged 85 and older were at even higher risk (RR = 1.99, 95% CI = 1.50–2.64).

Chronic use of nitrofurantoin and chronic use of other antibiotics were compared with any acute antibiotic use (chronic nitrofurantoin use, RR = 1.57, 95% CI = 1.08–2.27; chronic use of other antibiotics, RR = 1.12, 95% CI = 0.76–1.63). There was not a statistically significantly greater risk of lung injury with chronic nitrofurantoin use than with use of other antibiotics (RR = 1.35, 95% CI = 0.79–2.31).

Table 4. Demographic and Clinical Characteristics of Study Population According to Creatinine Clearance (CrCl), Calculated Using the Cockcroft-Gault Equation, with Overall Test for Association and Bonferroni-Adjusted Post Hoc Analyses Comparing CrCl Levels

Characteristic	No CrCl Measurement, n = 1,324	CrCl ≤30 mL/min, n = 1,157	CrCl 30–60 mL/min, n = 8,248	CrCl ≥60 mL/min, n = 2,692	Total, N = 13,421	*P*-Value
Treatment status, n (%)						
Antibiotic success	1,268 (95.8)	1,123 (97.1)	8,027 (97.3)	2,601 (96.6)	13,019 (97)	.16
Antibiotic failure	56 (4.2)	34 (2.9)	221 (2.7)	91 (3.4)	402 (3)	
Post hoc analysis *P*-value		Comparison	>.99	>.99		
			Comparison	>.99		
Age at diagnosis						
Mean ± standard deviation	74.1 ± 7.4	80.9 ± 7.4	74.0 ± 6.4	69.7 ± 4.6	73.7 ± 6.9	<.001
Median	72	81	73	68	72	
Interquartile range	68.0–79.0	76.0–87.0	69.0–78.0	66.0–72.0	68.0–78.0	
Range	65.0–99.0	65.0–99.0	65.0–100.0	65.0–92.0	65.0–100.0	
Post hoc analysis *P*-value		Comparison	<.001	<.001		
			Comparison	<.001		
Sex, n (%)						
Female	1,215 (91.8)	1,087 (93.9)	7,741 (93.9)	2,282 (84.8)	12,325 (91.8)	<.001
Male	109 (8.2)	70 (6.1)	507 (6.1)	410 (15.2)	1,096 (8.2)	
Post hoc analysis *P*-value		Comparison	>.99	<.001		
			Comparison	<.001		
Race and ethnicity, n (%)						
Non-Hispanic white	825 (62.3)	662 (57.2)	4,766 (57.8)	1,572 (58.4)	7,825 (58.3)	.001
Non-Hispanic black	61 (4.6)	110 (9.5)	771 (9.3)	178 (6.6)	1,120 (8.3)	
Hispanic	237 (17.9)	276 (23.9)	1,982 (24)	715 (26.6)	3,210 (23.9)	
Native American, Alaskan	0 (0.0)	0 (0.0)	7 (0.1)	3 (0.1)	10 (0.1)	
Asian, Pacific Islander	61 (4.6)	87 (7.5)	513 (6.2)	161 (6)	822 (6.1)	
Other	140 (10.6)	22 (1.9)	209 (2.5)	63 (2.3)	434 (3.2)	
Post hoc analysis *P*-value		Comparison	>.99	.13		
			Comparison	.01		
Education, n (%)						
Less than High School	75 (5.7)	107 (9.4)	771 (9.5)	239 (9.2)	1,192 (9.1)	<.001
High School Graduate	262 (19.0)	300 (26.4)	1,947 (24.1)	534 (20.6)	3,043 (23.3)	
More than High School	916 (69.2)	730 (64.2)	5,363 (66.4)	1,823 (70.2)	8,832 (67.6)	
Post hoc analysis *P*-value		Comparison	>.99	<.001		
			Comparison	<.001		
Vital status, n (%)						
Alive	1,015 (76.7)	707 (61.1)	7,211 (87.4)	2,496 (92.7)	11,429 (85.2)	<.001
Died	309 (23.3)	450 (38.9)	1,037 (12.6)	196 (7.3)	1,992 (14.8)	
Post hoc analysis *P*-value		Comparison	<.001	<.001		
			Comparison	<.001		
Treatment (days), n (%)						
Acute (<14)	1,238 (93.5)	1,113 (96.2)	7,968 (96.6)	2,571 (95.5)	12,890 (96.1)	.03
Chronic (≥14)	86 (6.5)	44 (3.8)	279 (3.4)	121 (4.5)	530 (3.9)	
Post hoc analysis *P*-value		Comparison	>.99	>.99		
			Comparison	.18		
1-year Charlson Comorbidity Index						
0	702 (53.0)	234 (20.2)	3,806 (46.1)	1,396 (51.9)	6,138 (45.7)	<.001
1–2	476 (36.0)	504 (43.6)	3,283 (39.8)	1,043 (38.7)	5,306 (39.5)	
≥3	146 (11.0)	419 (36.2)	1,159 (14.1)	253 (9.4)	1,977 (14.7)	
Post hoc analysis *P*-value		Comparison	<.001	<.001		
			Comparison	<.001		

Table 4 above presents the results of the comparison of treatment failure between CrCl categories (the third aim); 2.9% of participants with a CrCl of 30 mL/min or less, 2.7% of those with a CrCl of 30–60 mL/min, and 3.4% of those with a CrCl of 60 mL/min or greater experienced antibiotic failure.

The overall association between treatment failure and CrCl was not statistically significant (P = .16). There were no statistically significant differences between antibiotic failure and each of the CrCl categories when compared individually (P > .99 for all post hoc comparisons).

3.2.4.3 Discussion

Strengths of the study

The authors identified the following as strengths:

- Use of comprehensive electronic medical record and pharmacy prescription databases from a large integrated healthcare organization
- To the knowledge of the authors, this was the largest study to examine the association between nitrofurantoin and lung injury.
- Because published findings indicate that Kaiser Permanente Southern California health plan members reflect the socioeconomic and ethnic diversity of the census population, findings from this study may be broadly applicable to the general population of Southern California

Limitations of the study

The authors identified the following as limitations:

- Antimicrobial exposure was determined based on the health plan's pharmacy dispensing records; it cannot be stated with certainty that individuals given an antimicrobial actually ingested the medication.
- The study evaluated information from electronic medical records that rely on ICD-9 coding for the diagnoses of cystitis and lung injury
- Cure of cystitis was determined indirectly as absence of new antibiotic therapy within 21 days of the initial prescription of nitrofurantoin.
- Despite the matched-cohort design, the risk of channelling bias could not be eliminated. (Individuals who were sicker or for whom the prescriber may have felt to be at risk of pulmonary toxicity may have been prescribed antimicrobials other than nitrofurantoin).
- Finally, although matching was used to help control for confounding in the analysis, residual unmeasured fixed and time-varying confounding was not accounted for, which may have affected the associations found.

A statistically significant association between nitrofurantoin use and lung injury was not found, but this could have been the result of selection bias against a healthier control population of prescribing clinicians, a channeling effect that is reflected in the lower Charlson- Comorbidity Index of matched controls. Other techniques such as propensity matching and instrumental variable methods would strengthen further study of this association.

3.2.4.4 Conclusion

The authors state that the findings of this study add significantly to the current literature regarding the association between chronic nitrofurantoin exposure and pulmonary toxicity and the efficacy of nitrofurantoin in older adults with poor renal function. The results may be considered as additional evidence in future revisions of the AGS Beers criteria. Specifically, the findings support the current (2012) American Geriatric Society (AGS) Beers criteria recommendations against use of long-term nitrofurantoin suppression therapy because of risk of lung injury in older adults but refute recommendations to avoid the use of nitrofurantoin in older adults with poor renal function.

Comment: This study did not examine the risk of lung injury between the different CrCl groups treated with nitrofurantoin. The authors did not propose a CrCl cut-off point based on their findings.

3.2.5 Hoang et al (2016) – Updated nitrofurantoin recommendations in the elderly: A closer look at the evidence (Annex 7)

In 2015, the American Geriatrics Society (AGS) Beers Criteria Update Expert panel revised its recommendation to avoid use of nitrofurantoin in renal impairment from patients with a creatinine clearance (CrCl) of less than 60mL/min to those with a CrCl of less than 30mL/min, based on two retrospective studies that identified the safety and efficacy of nitrofurantoin in this population.

3.2.5.1 Purpose and Results

This article reviewed the studies (Bains *et al.* and Geerts *et al*.) and presented the key findings that resulted in the recommendation. These studies were considered by the MARC at the September 2015 meeting.

The key findings from these studies are summarised above in section 3.1

3.2.5.2 Conclusion

In conclusion the authors state that nitrofurantoin appears to achieve acceptable clinical cure rates and remains a relatively inexpensive choice for treatment of uncomplicated UTIs in patients with an estimated GFR (eGFR) of 50mL/min or less. Additionally, nitrofurantoin treatment was not associated with a higher risk of treatment failure in women with UTI and moderate renal impairment.

However, pulmonary adverse events because of nitrofurantoin use leading to hospitalisation were significantly associated with renal impairment.

3.2.6 Loh et al (2016) – Efficacy and safety of nitrofurantoin for treatment of cystitis in renal impaired patients (Annex 8)

3.2.6.1 Purpose

To determine if treatment of cystitis with nitrofurantoin in renal impaired patients was associated with lower cure rates and if higher rates of adverse events were observed in renal impaired patients.

3.2.6.2 Methods

A cohort of 272 patients from Changi General Hospital treated for cystitis with nitrofurantoin from 2011 to 2014, identified from electronic hospital records, were analysed.

Renal impairment was defined as CrCl <60 mL/min and non-renal impairment as CrCl ≥60 mL/min. Cure rates were based on clinical and/or microbiological cure.

Clinical cure of cystitis was defined by the successful discontinuation of a course of nitrofurantoin, no other antibiotics for treatment of cystitis was prescribed 2 weeks from the start of a course of nitrofurantoin and no further documentation of cystitis symptoms.

Microbiological cure was defined as a repeat negative urine culture. Adverse events associated with nitrofurantoin were also recorded. The association between cure rates and renal impairment was determined with the $^{x}2$ test of independence.

3.2.6.3 Results

Cure rates between patients without renal impairment and patients with renal impairment were similar (cure rates of 79.4% in non-renal impaired patients vs 79.5% in renal impaired patients, X2 (1, n = 272) =0.004, p = 0.977).

However, no adverse events were found to be associated with nitrofurantoin, possibly as adverse events were poorly documented.

3.2.6.4 Conclusion

Nitrofurantoin was able to achieve satisfactory cure rates in renal impaired patients with CrCl < 60 mL/min, although further studies in larger cohorts would have to be conducted to determine if higher rates of adverse events were observed in renal impaired patients.

Comment: The authors of this abstract did not suggest a lower limit of creatinine clearance (CrCl) that nitrofurantoin could be used in. They only stated that the cure rates between patients with CrCl >60mL/min and <60mL/min were similar.

3.2.7 Ingalsbe et al (2015) - Effectiveness and safety of nitrofurantoin in outpatient male veterans (Annex 9)

3.2.7.1 Methods

This was a retrospective study of male veterans who were dispensed a prescription of nitrofurantoin dating from 1 January 2004 to 31 July 2013 in the Veteran Affairs (VA) Western New York Healthcare System. Data were collected through a retrospective chart review.

The purpose of the study was to assess the safety and effectiveness (clinical cure) of nitrofurantoin in male veterans treated for urinary tract infections (UTIs) with varying degrees of renal impairment in the outpatient setting.

The study aimed to determine a creatinine clearance (CrCl) threshold to achieve an 80% cure rate. It also sought to determine a difference if the patient had a UTI with Gram-positive versus Gram-negative or mixed infection.

Inclusion criteria

- Male patients over the age of 18 years who sought care in the VA Western New York Healthcare System and received nitrofurantoin for the treatment of a UTI in the outpatient setting.
- Patients were included if they had signs and symptoms of cystitis or an infection in the lower urinary tract. Patients with a catheter-associated UTI were also included.

Cultures were collected for all patients; however, lack of cultures did not lead to exclusion.

Exclusion from the study

- Patients were excluded from the study if they received concurrent antibiotics in addition to nitrofurantoin

Exclusion from the effectiveness analysis

Patients were excluded from the effectiveness analysis if they were prescribed nitrofurantoin for:

- chronic suppressive therapy
- prophylaxis
- posturological procedure
- prostatitis
- pyelonephritis

Patients were also excluded from the effectiveness analysis if they:

- had resistant urinary isolates (resistant cultures or known non-susceptibility to nitrofurantoin)
- or did not have clear signs and symptoms of a UTI (defined as dysuria, urinary frequency, fever, rigors, flank pain, or nausea)

Patients with an indwelling catheter could also have symptoms including suprapubic pain, urgency, rigors, or an acute mental status change with no alternative diagnosis.

Exclusion from the safety analysis

- Patients with an adverse reaction clearly related to another medication were excluded from the safety analysis.

Study endpoint

Clinical cure was defined as:

- No signs or symptoms of a UTI for 14 days after stopping nitrofurantoin, without other antibiotic use.

If a second antibiotic was prescribed subsequently during this time period for a UTI, treatment with nitrofurantoin was considered a failure.

Secondary endpoint

- The occurrence of Adverse Drug Events (ADEs) related to nitrofurantoin therapy.

Patients were divided into three groups based on their creatinine clearance (CrCl) (CrCl < 40 ml/min, CrCl 40–59 ml/min, and CrCl ⩾ 60 ml/min) to determine the presence of ADEs with various levels of renal function.

ADEs included gastrointestinal distress, headache, peripheral neuropathy, rash, acute pulmonary reaction, hepatotoxicity, haemolytic reaction, or miscellaneous. Patients were followed for ADEs for 7 days after completion of nitrofurantoin.

Data Collection

Medical and laboratory data were collected by chart review from the VA's computerized patient record system. Data collected included age, height, weight, serum creatinine, liver function enzymes (aspartate aminotransferase, alanine transaminase), reported signs and symptoms of UTIs, comorbidities, presence of a catheter, type of catheter if applicable, pH of the urine, type of bacteria isolated with susceptibilities, and the formulation of nitrofurantoin dispensed as well as the directions and duration of treatment.

Demographics and laboratory data were collected closest to the date that the nitrofurantoin prescription was written, but no greater than 6 months apart from the infection.

Statistical Analysis

Bivariate analyses followed by multivariate analyses were performed between patients experiencing clinical cure and those who did not, to determine factors significantly impacting effectiveness. For continuous data, an independent sample student's t test was used to determine significance and for categorical data, a chi-square test was used.

All values from the multivariate with a p ≤0.05 were included in a multivariate logistic regression analysis. Variables were eliminated in a backwards fashion, with the least significant variable eliminated and a new model created in a stepwise fashion. Models were built controlling for significant factors to determine a creatinine clearance (CrCl) threshold to achieve an 80% clinical cure rate for gram-positive, gram-negative and mixed infections.

Analysis of variance was used to determine any significant difference in adverse drug events (ADEs) across the three creatinine clearance (CrCl) groups.

Comment: Nitrofurantoin susceptibilities were reported during the study period to be: E.coli (97-100%), Enterococcus faecalis (98-100%) and Enterococcus faecium (56-71%).

3.2.7.2 Results

The inclusion criteria were met by 801 patients for the safety analysis and 485 for the effectiveness analysis.

The majority of patients, 571 patients were prescribed Macrobid 100mg twice daily, 164 patients received macrocrystals (50mg-100mg four times daily), six patients received the suspension and 60 patients received Macrodantin (50-100mg four times daily).

Comment: According to the FDA label, Macrobid is a prolonged-release nitrofurantoin capsule that only needs to be dosed twice daily, whereas macrocrystal, Macrodantin and suspension forms need to be given more frequently (four times daily) for treatment.

Baseline characteristics and comorbidities of patients included in the effectiveness analysis are shown in table 1 below.

Table 1. Demographics and comorbidities: bivariate analysis of patients included in the effectiveness analysis.

Characteristic	Total cohort	No clinical cure $n = 110$	Clinical cure $n = 375$	p value
Age (years)	73.32 ± 11.30	75.37 ± 12.37	72.71 ± 10.91	**0.028**
Height (m)	1.75 ± 0.08	1.75 ± 0.09	1.76 ± 0.07	0.37
Weight (kg)	86.82 ± 20.79	82.23 ± 17.23	88.18 ± 21.55	**0.0074**
Serum creatinine (μmol/L)	98.12 ± 37.12	107.00 ± 44.20	94.58 ± 35.36	**0.0056**
Creatine clearance (ml/min)	66.11 ± 26.78	59.90 ± 27.54	67.93 ± 26.31	**0.0037**
Aspartate aminotransferase (units/L)	23.02 ± 16.02	23.62 ± 18.22	22.83 ± 15.27	0.66
Alanine transaminase (units/L)	26.13 ± 19.34	26.27 ± 24.03	26.08 ± 17.68	0.93
Postherpetic neuralgia	0.62% ($n = 3$)	0.9% ($n = 1$)	0.5% ($n = 2$)	0.66
Neuropathy	17.94% ($n = 87$)	15.5% ($n = 17$)	18.7% ($n = 70$)	0.44
Prior pulmonary reaction	0.41% ($n = 2$)	0.9% ($n = 1$)	0.4% ($n = 1$)	0.36
Chronic obstructive pulmonary disease	21.65% ($n = 105$)	15.5% ($n = 17$)	23.5% ($n = 88$)	0.073
Liver dysfunction	5.57% ($n = 27$)	4.6% ($n = 5$)	5.9% ($n = 22$)	0.60
Diabetes mellitus	37.32% ($n = 181$)	38.2% ($n = 42$)	37.1% ($n = 139$)	0.83

<u>Comment:</u> Total number of patients in the effectiveness analysis n=485. There was a significant difference between the group of patients experiencing cure and no cure regarding age, weight and creatinine clearance in the bivariate analysis (p <0.05).

- Of the UTI signs and symptoms that were reported to be diagnostic of UTI, only dysuria demonstrated significance in the bivariate analysis. Of those who experienced clinical cure, 18.4% experienced dysuria versus 30.9% who did not experience a cure (p =0.003).
- There was no significant difference in urine pH between the two groups (6.14± 0.75 versus 6.13±0.69, p=0.90).
- Patients were treated for approximately the same duration of treatment between the success and failure groups; 8.58 ± 3.57 days versus 9.26 ± 6.92 days (p = 0.28).

- Approximately 32% of the population had a catheter at the time nitrofurantoin was prescribed. There was a significant difference between the different types of catheters and those with an un-instrumented urinary tract There was no statistical difference when comparing cure rates with the presence versus absence of a catheter (p = 0.089). Of those who experienced clinical cure with nitrofurantoin, 29.6% had a catheter of any type versus 70.4% who had no catheter. For clinical failure, 38.2% had a catheter and 61.8% did not have a catheter (p = 0.089).

Significant factors in the effectiveness analysis (Age, weight, creatinine clearance and Gram-stain) were built into a multivariate logistic regression model to determine impacting the success of treatment with nitrofurantoin.

A backwards elimination of the least significant factors was performed to provide a stable model. Age (p = 0.96) and then weight (p = 0.051) were eliminated, leaving individual CrCl (p = 0.030) and Gram stain of urine culture (p = 0.0013) to be included in the final model.

The model was rebuilt with Gram stain (p = 0.0004) and individual CrCl (p = 0.0032). In this final model, the unit odds ratio for CrCl was 1.013 (95% CI 1.004–1.023), indicating that for every 1 ml/min increase in CrCl, the odds of clinical cure also increased by 1.3%; this was a linear relationship.

Individual prediction profiles were built to determine what CrCl breakpoint would be required to establish a cure rate of 80% for the Gram stain in the urine culture:

- For urine cultures with only Gram-negative organisms, primarily composed of *E.coli* in this patient population, the minimum CrCl required to achieve at least an 80% cure rate was 58 ml/min
- For cultures with only Gram-positive organisms (predominately *Staphylococcus aureus* or *Enterococcus*), a CrCl of at least 98 ml/min was needed
- The cut-off for mixed Gram positive and Gram negatives was > 100 ml/min
- for negative cultures 63 ml/min
- and for patients who did not get a urine culture 32 ml/min.

Of the patients who had a recurrence or reinfection, 123 patients had repeat urine cultures. A total of 74 patients had infection with the same bacteria with which they were infected prior to the nitrofurantoin treatment. When percentage failure was analysed by CrCl groups, 9 failed (12.12%) in CrCl $\leqslant$ 40 ml/min, 27 failed (36.49%) in the CrCl group of 40–59 ml/min, and 51.35% failed in those with CrCl $\geqslant$ 60 ml/min (p = 0.70).

Safety analysis

The incidence of adverse drug events (ADEs) across the different creatinine clearance (CrCl) categories is documented in table 2 below.

Table 2. Impact of creatine clearance on adverse drug events rate: percentage of total adverse drug events.

Event	Total cohort n = 801	CrCl < 40 ml/min	CrCl 40–59 ml/min	CrCl ⩾ 60 ml/min	p value
Gastrointestinal distress	0.87% (n = 7)	0.12% (n = 1)	0.25% (n = 2)	0.5% (n = 4)	0.90
Peripheral neuropathy	0.50% (n = 4)	0.25% (n = 2)	0.12% (n = 1)	0.12% (n = 1)	0.54
Rash	0.25% (n = 2)	0.00% (n = 0)	0.00% (n = 0)	0.25% (n = 2)	0.50
Acute pulmonary reaction	0.38% (n = 3)	0.00% (n = 0)	0.25% (n = 2)	0.12% (n = 1)	0.53
Hepatotoxicity	0.50% (n = 4)	0.00% (n = 0)	0.25% (n = 2)	0.25% (n = 2)	0.67
Hemolytic reaction	0.13% (n = 1)	0.00% (n = 0)	0.00% (n = 0)	0.12% (n = 1)	0.75
Other	2.75% (n = 22)	0.25% (n = 2)	0.75% (n = 6)	1.75% (n = 14)	0.87

CrCl, creatinine clearance.

Comment: Number of patients in the safety analysis n=801. Statistical significance was not demonstrated for any of the reported ADEs across the different CrCl categories.

3.2.7.3 Discussion

The authors state that their data suggest that using a CrCl cut-off of 60 ml/min is reasonable to achieve effectiveness in men with UTIs. Nitrofurantoin is primarily used to treat Gram-negative UTIs, particularly those caused by *E.coli*, andthese models showed that a CrCl around 58 ml/min or above is needed to achieve a cure rate of at least 80%.

The positive correlation of clinical cure rates with CrCl suggests that limiting the use of nitrofurantoin to patients with better renal function is appropriate to ensure adequate cure rates. The mechanism behind this correlation is unclear, but may be related to the lower urinary concentrations of nitrofurantoin in patients with reduced CrCl that have been demonstrated in other studies [*Sachs et al.* 1968].

Patients with no growth in their urine cultures required a CrCl in the same range as Gram-negative cultures (63 ml/min) to achieve 80% clinical cure. It is unclear if these patients had no growth in their cultures because they did not have a bacterial UTI, or if negative cultures were a result of poor urine collection technique or undocumented pre-treatment with antibiotics before the culture was obtained.

UTIs caused by Gram-positive organisms or mixed Gram-positive and Gram-negative organisms required a much higher CrCl (around 100 ml/min or higher) to achieve similar rates of clinical cure. This suggests that nitrofurantoin may not be as effective in this group of organisms, requiring higher urinary concentrations to achieve clinical cure. Another possibility is that these patients had UTIs that were more complicated, potentially leading to lower cure rates regardless of treatment.

When Gram-positive infections were further analysed, 24% of catheterized patients had a Gram-positive infection. In the Gram-positive group 36.42% had an enterococcal infection, and 54.31% had a staphylococcal infection. It seems that most of the failure was driven by the staphylococcal isolates (25% of total failures) and enterococcal isolates (15.45% of total failures). Further studies would be needed to evaluate the specific etiological factors impacting clinical cure in these patients.

There was also a significant group of patients in this study who were treated empirically for UTIs without obtaining a urine culture. This group appears to be less affected by lower CrCl, maintaining 80% or greater cure rates to a CrCl of 32 ml/min. The exact reasons for this are unclear, but it could be due to selection bias in determining from which patients to obtain urine cultures. It is plausible that the providers may have been more apt to obtain pre-treatment cultures on sicker patients, or those with greater likelihood of failure, such as those with recurrent infections, while fewer cultures were obtained on patients who had lower risk of failure with empirical treatment. This could have made the group without urine cultures appear more responsive to nitrofurantoin therapy.

A previous retrospective review looked at 356 patients and found similar cure rates in patients with an estimated GFR $\leqslant$ 50 ml/min (renal impairment) compared with patients with an estimated GFR > 50 ml/min (control group). Unlike this study, the effectiveness was predominantly assayed in women. The renal impairment group consisted of only 16% male patients [Bains et al. 2009].

Women with uncomplicated UTIs are generally more responsive to treatment, while UTIs in men are, by definition, complicated [Gupta et al. 2011]. Complicated UTIs are more often associated with anatomic abnormalities or instrumentation, and are typically more difficult to treat. These differences could have contributed to the study failing to find a difference in cure rate with decreased renal function. Thus, patients with UTIs that are easier to treat may be able to obtain clinical cure even with lower CrCl, while those with more complicated infections require better renal function to achieve adequate therapeutic levels of nitrofurantoin in the urinary tract.

CrCl did not have a significant impact on the rate of ADEs with nitrofurantoin. However, the number of ADEs that was reported in our study was small. This is in contrast to an earlier report conducted in women, suggesting an increased rate of pulmonary reactions in patients with lower CrCl [Hooton *et al.* 2010]. Another study, similar in size to our study, indicated no difference in ADEs with different CrCl groups (GFR ⩽ 50 ml/min *versus* > 50 ml/min) [Bains *et al*. 2009]. While there is a potential for increased accumulation of nitrofurantoin with lower CrCl, this has not been shown to be significant in this study from a safety standpoint.

Study limitations

The authors identified the following as limitations of this study:

- Primarily white male veteran population, which may limit external validity.
- The retrospective nature of the study means there was potential for lack of documentation of administration of the drug, reporting of Adverse Drug Events (ADEs), and early discontinuation of therapy by the patient.
- The timing of the urine culture relative to the initiation of therapy was not recorded. This may have implications, particularly for the group of patients with no growth in their urine culture, as it may be possible that the patient first took his first dose of antibiotic before submitting a urine culture.
- All calculation of renal impairment were performed using the Cockcroft-Gault equation. Different results may be seen if other measures of renal function are utilized.

3.2.7.4 Conclusion

The authors state that the data from this study support a creatinine clearance (CrCl) cut-off of 60mL/min for the use of nitrofurantoin to treat outpatient UTIs in men, based on the lower rates of clinical cure seen below this threshold for Gram-negative infections.

4.0 DISCUSSION AND CONCLUSIONS

The MHRA recommendation in 2014 to reduce the renal contraindication cut-off point to an eGFR of 45mL/min/1.73m^2 for most patients in the UK was based on the results from *Oplinger and Andrews*, and *Geerts et al* (8). At the September 2015 MARC meeting these studies were included as part of the review.

The MARC commented that the overall data on efficacy in patients with renal impairment was limited and although no statistical difference in efficacy was noted there were limitations to the data including sample size. Similarly no statistically significant difference in the rate of adverse effects was seen in patients with renal impairment, however, there was a trend to an increased risk and the sample size was small.

Since then, a recent PubMed literature search yielded five new retrospective studies, published between late 2015 through to 2018.

Ingalsbe et al examined the effectiveness of nitrofurantoin for the treatment of UTI in outpatient male veterans (n=485) and determined a minimum CrCl to achieve an 80% cure rate for gram-negative infections (predominantly *E.coli*) of 58mL/min. Gram-positive and mixed infections required even higher CrCl to achieve an 80% cure rate (~100 mL/min each). The authors also found that nitrofurantoin ADRs did not vary according to CrCl.

Santos et al examined nitrofurantoin treatment failure rates between CrCl values in patients over 65 with a diagnosis of cystitis. The authors found no statistically significant difference in treatment failure rates between patients with CrCl ≤30mL/min, 30-60mL/min and ≥60mL/min (n=13,421).

Ahmed et al compared the risk of adverse outcomes in patients aged ≥65 presenting to primary care with a UTI, by eGFR (divided into groups eGFR >60mL/min, 45 – 59, 30 – 44 and <30 respectively) and

empirical prescription of nitrofurantoin versus trimethoprim. The authors found that nitrofurantoin use was not associated with greater odds of any adverse outcomes including: reconsultation + re-prescription (i.e. treatment failure), hospitalisation for UTI, sepsis or AKI within 14 days following UTI, or death within 28 days following UTI in patients with eGFR < 60mL/min compared with trimethoprim use (n=7484 nitrofurantoin patients).

Loh et al found similar cure rates between patients with CrCl <60mL/min and those with CrCl ≥60mL/min treated with nitrofurantoin for cystitis at Changi General Hospital, however the number of patients included in the cohort was low (n=272). Similarly, *Cunha et al* noted that nitrofurantoin was effective in patients with CrCl values between 30 - 60mL/min for the treatment acute uncomplicated cystitis, however there were only 26 patients included in that chart review. The authors of both studies reported no adverse reactions to nitrofurantoin.

Additionally, a systematic review in 2017 (*Muller et al*) did not yield any robust information on nitrofurantoin's efficacy and toxicity in UTI prophylaxis for patients with renal insufficiency.

After reviewing the Australian and US product information for nitrofurantoin in 2019, they still appear to be aligned with New Zealand's renal impairment contraindication of <60mL/min. The TGA have no plans to review this topic.

Finally, the CARM data does not include enough information to analyse the frequency of ADR reports based on renal function, however the data shows that serious adverse reactions continue to be reported for nitrofurantoin.

The advice sought from the Committee is whether the new studies provide additional evidence that warrants a change to the current contraindication point of CrCl <60mL/min.

5.0 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the new evidence warrants a change to the current contraindication point for nitrofurantoin use in renal impairment (creatinine clearance [CrCl] <60mL/min).
- If a change to the contraindication point is warranted, what the new cut-off for creatinine clearance (CrCl) should be.
- How this issue should be communicated to healthcare professionals and consumers.

6.0 ANNEXES

Annex 1. Nitrofurantoin use in renal impairment – September 2015 MARC paper

Annex 2. New Zealand *Nifuran* data sheet – (10 July 2017)

Annex 3. Ahmed *et al.*

Annex 4. Muller et al.

Annex 5. Cunha *et al.*

Annex 6. Santos *et al.*

Annex 7. Hoang *et al.*

Annex 8. Loh *et al.*

Annex 9. Ingalsbe *et al.*

7.0 REFERENCES

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