Drug Corner

Nitrofurantoin : Old Molecule Revisited

Prem Kumar[1]

Urinary tract infections (UTIs) are one of the most common bacterial infections affecting nearly 150 million people each year worldwide. The main goal of the UTIs therapy is to provide symptomatic relief for the patients. Several antibiotics are available for the management of UTIs. Nitrofurantoin is unique and first-line antibiotic approved for the treatment of UTI. It a broad-spectrum bactericidal antibiotic that, through a complex mode of action which is not completely understood, affects both Gram-negative and Gram-positive bacteria. Nitrofurantoin macro-crystalline formulations has several advantages over initially developed microcrystalline form with less side effects. The macro-crystalline formulations of nitrofurantoin has replaced the initially developed micro-crystalline because of its advantages like low interaction with food, better tolerance and lesser side effects. Many clinical studies have proven that nitrofurantoin is an effective antibiotic and compares well with the other antibiotics for the long-term prophylaxis. It is indicated for the treatment of lower UTI, recurrent UTI, uncomplicated UTI or acute uncomplicated cystitis in women, etc. Nitrofurantoin was safe and effective for the treatment of UTIs in children, diabetes and in pregnant women. Several guidelines such as IDSA, NICE and SIGN have recommended nitrofurantoin for the treatment of UTI. The present review discusses the mechanism of action, antimicrobial spectrum, pharmacology, safety profile and therapeutic use of nitrofurantoin, including recent data which highlight its role in the management of urinary tract infection.

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Key words **: Urinary tract infection, Nitrofurantoin, Macro-crystalline Nitrofurantoin, Recurrent UTIs, Cystitis.**

Urinary tract infections (UTIs) are one of the most common bacterial infections affecting nearly 150 million people each year worldwide.[1] UTI occurs due to the presence of microbial pathogens within the urinary tract. Depending on the site of infection it is classified as cystitis (bladder), pyelonephritis (kidney) or bacteriuria (urine).[2]While, clinically UTI is categorized as complicated or uncomplicated UTI.[1]

UTI is more prevalent in women as compared to menand is the most common concern for women.[3]Approximately, 60% of the adult women and 10% of the post-menopausal women would be presented with at least one symptomatic UTI in their life.[4] Also, the UTIs prevalence increases with age such that it increases 10 to 20% in women age more than 65 years. All these makes UTI an important concern in the increasingly aging population. UTI leads to 8.6 million health care visits and around 1.6 billion dollars of an estimated costs.[3]The key clinical classification of UTI according to the most recent guidelines is depicted below[4] (Table 1).

PREDISPOSING FACTORS :

The most common diagnostic symptomsof UTIs are change in urination frequency, dysuria, urgency, and presence or absence of vaginal discharge, these symptoms present differently in older women (Table 2).[3]

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Editor's Comment :

- **Nitrofurantoin is a broad spectrum antibiotic with complex mode of action.**
- **It is recommended as a first-line antibiotic for the treatment of UTI.**
- **Macro-crystalline formulations of nitrofurantoin has several advantages with fewer side effects.**
- **It is indicated for LUTI, recurrent UTI, catheter associated UTI, multi drug-resistant strains UTI and acute uncomplicated cystitis in women.**
- **Nitrofurantoin is also indicated for treatment of UTI in special population such as pregnant women, diabetes and children.**

PATHOGENESIS :

Urinary tract infection is a complex event. The infection arises when the bacterial virulence mechanisms overcome the host defense mechanisms. In the pathogenesis of UTI, bacterial adhesion to the uro-epithelium is an important step.[5]Gram-positive and Gram-negative bacteria, as well as certain fungi are the causative agents for UTIs. Out of which the most common causative agents for both the complicated as well as for uncomplicated UTIs is *Escherichia coli.*[1]

MANAGEMENT :

There are several antibiotics available for management of UTIs. The main goal of the UTIs therapy involves symptomatic relief for the patients. For the appropriate clinical response antibiotic therapy which achieves higher concentration in urinary tractis recommended. For cystitis,

Table 1 — *Key classification of UTIs*[4]

Classification	Definition
Uncomplicated UTI	A UTI where there are no relevant functional or anatomical abnormalities in the urinary tract, no relevant kidney function impairment, and no relevant concomitant diseases promoting the UTI or risk or developing serious complications
Acute uncomplicated cystitis	A lower UTI in which the acute symptoms involve only the lower urinary tract, for example, urgency, painful voiding (dysuria), pollakiuria, and pain above the symphysis
Acute uncomplicated pyelonephritis	An upper UTI with persistent symptoms including flank pain, flank tenderness, or fever (>38°C)
Asymptomatic bacteriuria	A positive urine culture (>10^5 colony-forming units/mL) in the absence of urinary
Recurrent uncomplicated UTIs	A recurrent UTI refers to the occurrence of ≥2 symptomatic episodes within 6 months or ≥3 symptomatic episodes within 12 months

UTI, urinary tract infection

Table 2 — *Predisposing risk factors for UTI*[5]

Patient population	Risk factors
Premenopausal women of any age	• Diabetes • Diaphragm use, especially those with spermicide • History of UTI or UTI during childhood • Mother or female relatives with history of UTIs
Postmenopausal and older adult women	• Estrogen deficiency • Functional or mental impairment • History of UTI before menopause
Men and women with structural abnormalities	Extrarenal obstruction associated with congenital anomalies of the ureter or urethra, calculi, extrinsic ureteral compression, or benign prostate hypertrophy Intrarenal obstruction associated with nephrocalcinosis, uric acid nephropathy, polycystic kidney disease, hypokalemic or analgesic nephropathy, renal lesions from sickle cell disease

response occurs within 24 hours and in 48-72 hours for pyelonephritis. The selected antibiotic should have lesser impact on normal bacterial flora of vagina. Antibiotic which has less adverse events should be used for the treatment.

Hydration is often done which removes the infected urine by frequent bladder emptying during the UTI management. Depending on the susceptibility of *E coli* and other uropathogens, therapy was initiated. The recommended first-line antibiotics for the treatment of UTI includes nitrofurantoin, trimethoprim/sulfamethoxazole, fluoroquinolones, and fosfomycin.[5]

Nitrofurantoin has good efficacy, used as first-line agents for UTI in pregnancy, etc. and susceptible towards most of the uropathogens compared with other antibiotics.[3]

NITROFURANTOIN

Nitrofurantoin is a unique antibiotic approved by FDA in 1953 for the treatment of uncomplicated lower UTI.[6] It belongs to the nitrofuran family, characterized by a hydantoin ring with a nitro-substituted furanyl side chain (Fig 1).[7]It is effective against both gram-positive and gram-negative organisms.[6]

Mechanism of action :

The exact mechanism of nitrofurantoin is not fully understood and presumably multifactorial.[8] It uses various mechanisms to achieve an antimicrobial effect.[6] The nitrogroup coupled onto the heterocyclic furan ring is the specific active site of the drug.[7] It gets activated inside the bacteria by rapidly reducing to 'highly reactive electrophilic' reactive metabolites by flavoproteins (Nitrofuranreductase).[8, 9]

These reactive intermediates inhibit ribosomal proteins, DNA, RNA, metabolic enzymes, and other intracellular components that involve in bacterial carbohydrate metabolism at three points in the Krebs cycle as well as interfering with cell wall synthesis.[7] The multiple mechanism for nitrofurantoin responsible for the low resistance against it.[9]

Antimicrobial spectrum :

Nitrofurantoin is a broad spectrum antibiotic. It is effective against most of the gram-negative, gram-positive, and anaerobic bacteria. It hasbactericidal activity against most of the common uropathogens, including *Escherichia coli, Enterococci, Klebsiella, Staphylococcus saprophyticus, and Enterobacter*. Shigella, *Salmonella, Citrobacter, Neisseria, Bacteroides,* group B *streptococcus, Staphylococcus aureus, and Staphylococcus epidermidis* are also included in its spectrum of susceptibility.[6]

Pharmacology :

Nitrofurantoin has 80% bioavailability in the healthy adults and is well absorbed in gastrointestinal tract.[6] It is mainly excreted in the urine and bile with urinary excretion rate of 40%.[7] It achieves its therapeutically active concentrations in the lower urinary tract and does not reach to its therapeutic concentrations in the other sites of the body.[10]

As compared to other drugs nitrofurantoin is relatively safer. Nausea, vomiting, loss of appetite and diarrhea were few commonly reported side effects. While, the newer macro-crystalline formulations has less side effects than the older microcrystalline one.[7]

Nitrofurantoin macro-crystalline vs. microcrystalline formulations:

Initially, nitrofurantoin was developed in microcrystalline form as nitrofurantoin monohydrate. But, recently macro-crystalline formulations has replaced

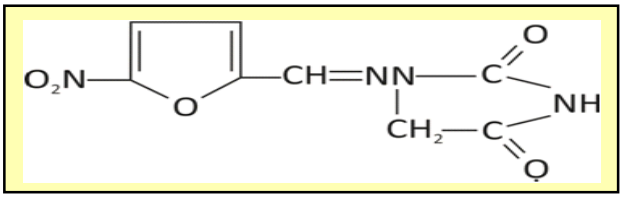

Fig 1 — Chemical structure of Nitrofurantoin[7]

Macro-crystalline formulations advantages: [11]

- **Less side effects.**
- **Slower absorption rate improved gastrointestinal tolerance.**
- **Slower excretion rate. [microcrystalline formulation has 50% higher excretion rate]**
- **Administration with food:**
  - ✓ **Increase exposure to uropathogens**
  - ✓ **Minimizes side effects**
  - ✓ **Increases absorption rate**
- **Higher plasma concentrations (1.8 mg/L) [while microcrystalline formulation has 0.99 mg/L] which increases up to 4.6 mg/L with food.**

microcrystalline formulations due to the unwanted gastrointestinal side effects seen withmicrocrystalline formulation because of its rapid absorption.[10]

Indications :

The recommended doseof nitrofurantoin for UTI is 50 mg or 100 mg four times a day.[7] Till 1970swhen trimethoprim-sulfamethoxazole and newer beta-lactam antibiotics became available,nitrofurantoin was widely used for the treatment of LUTIs. But recently, several major guidelines have recommended nitrofurantoin as the first-line therapy for the treatment of uncomplicated LUTIs.

Use of nitrofurantoin was re-started with increasing resistance to newer antibiotics corresponding with increasing prevalence of extended-spectrum beta-lactamase (ESBL) producing bacteria.The treatment and prophylaxis of UTI was the primary use of nitrofurantoin.It shows equivalent results as that of comparators in themeta-analysis for clinical cure of uncomplicated UTI. Clinical studies demonstrated that nitrofurantoin is an effective antibiotic and compares well with the other antibiotics for the long-term prophylaxis.[6] Nitrofurantoin is used for:

- LUTI
- Recurrent UTI
- Uncomplicated UTI in women
- Acute uncomplicated cystitis in women
- Multi-resistant strains UTI
- Nosocomial vancomycin-resistant *enterococci* (VRE) or VRE catheter-associated bacteriura
- Catheter-associated bacteriuria
- *E.coli* against Non-ESBL
- Alternative for ESBL-producing *E.coli*-related LUTI

In special population :

- Bacteriuria in pregnancy
- UTI in pediatrics
- Bacteriuria in neurogenic bladder patients
- First line management of UTI in diabetes patients-100 mg three times daily for 5 days[12]

CLINICAL EVIDENCES :

- **Assessing safety and efficacy of nitrofurantoin for lower urinary tract infection (LUTI)[13]**

One of the most common life threatening infection is the urinary tract infection (UTI). For the treatment of UTI, various antibiotics are used but, increase in the resistance among pathogenic organisms is the major concern in choosing effective treatment. Bansal N, et al., conducted the study to investigate the efficacy and safety of nitrofurantoin in the treatment of LUTI.

The open-label, single-arm study enrolled 70 patients diagnosed with LUTI. Enrolled subjects received 100 mg nitrofurantoin two times a day for five days after which the efficacy was evaluated by the loss of symptoms and eradication of organism on culture.

The sensitivity of the nitrofurantoin was reported to be 84.3%. While, the highest sensitivity was observed with Proteus (87.5%), followed by *E. coli* (84.7%), *Staphylococcus aureus* (83.3%), *Klebsiella* (70%), amongst all the pathogenic organisms. On the repeat culture, 91.5% was the bacterial eradication rate (Fig 2). While, nausea was the common reported adverse effect.

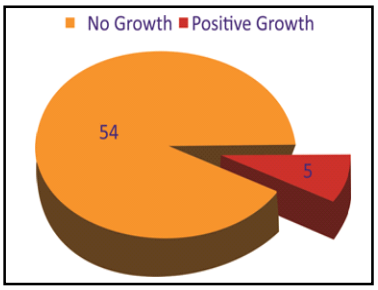

Fig 2 — Bacterial eradication on repeat urine culture

The study concluded that nitrofurantoin was safe and effective in the treatment of LUTI with lowest reported resistance.

- **Evaluating the safety and efficacy of nitrofurantoin in comparison with the ciprofloxacin in the UTI patients[9]**

The prospective study was conducted by Kaur R *et al.*, with an aim to evaluate the efficacy and tolerability of nitrofurantoin and ciprofloxacin in the UTI patients.

The prospective, open, randomized, parallel-group, comparative study enrolled 60 patients diagnosed with acute/uncomplicated or recurrent UTI. The subjects were randomized (1:1) to receive nitrofurantoin 100mg BD or ciprofloxacin 500mg BD for 5 days for uncomplicated UTI and for 15 days in case of recurrent UTI. Bacteriological response was recorded by evaluating urine culture at the end of the study.

The study reported that *E. coli* (80%) was the most common uropathogen related with uncomplicated UTI, while, *Klebsiella, Staphylococcus aureus, Providencia* were the other organisms detected (3.33%). Post treatment urine culture, significant difference was observed between the two groups in the growth of micro-organisms (P= 0.017) (Fig 3).

The results suggests that nitrofurantoin is more effective than ciprofloxacin as it leads to statistically significant bacteriological improvement on urine culture. Increased antibiotic resistance of ciprofloxacin amongst the uropathogens is responsible for less bacteriological improvement on the urine culture.

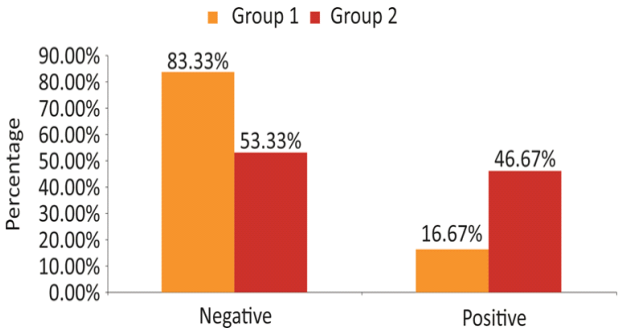

Fig 3 — Posttreatment culture results[9]

- **Investigating the first-line and second-line therapies for the treatment of uncomplicated UTI[14]**

The retrospective study was conducted to evaluate the most effective and relevant method for the treatment of uncomplicated UTIs.

A retrospective, clinical study analyzed antimicrobial susceptibility patterns from the 10417 collected urinary isolates.

The study results indicate that nitrofurantoin has significantly greater susceptibility to *E. coli* urine isolates with an average resistance rate of 2.3% than ciprofloxacin, levofloxacin and co-trimoxazole (P<0.05). *E. coli* resistance to nitrofurantoin ranged from 0.8% in 2003 to 3.3% in 2007 as compared to ciprofloxacin and levofloxacin which ranged from 20% to 25% (Fig 4).

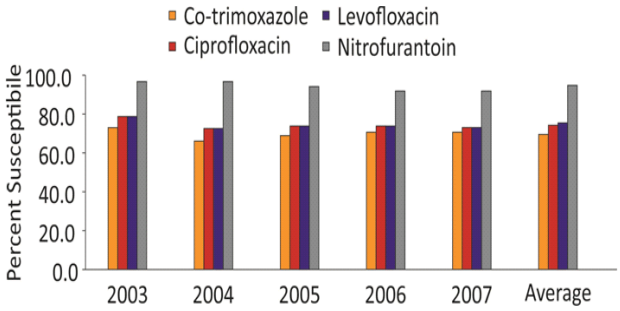

Fig 4 — Susceptibility patterns of E. coli from 2003 to 2007[14]

In conclusion, study demonstrates that nitrofurantoin is an acceptable treatment for uncomplicated UTIs, and should be considered for the first-line therapy.

- **Comparing one-day and seven-day nitrofurantoin regimen for the treatment of asymptomatic bacteriuria in pregnancy[15]**

Asymptomatic bacteriuria prevalence in pregnancy ranges from 2-11%. Most of the antibiotics prescribed for the treatment of asymptomatic bacteriuria in pregnancy are resistant to uropathogens. But, little or no modifications in the bacterial resistance was observed with nitrofurantoin. Thus, the study was conducted to evaluate the efficacy of 1-day and 7-day nitrofurantoin regimen in eliminating asymptomatic bacteriuria during pregnancy.

A multicenter, double-blind, randomized, placebo controlled, noninferiority trial included 778 pregnant women with asymptomatic bacteriuria. The enrolled subjects were randomized to receive either a 1-day or a 7-day course of 100 mg nitrofurantoin twice daily.

Primary outcome : bacteriologic cure after the treatment.

Secondary outcome: incidences of symptomatic UTI, preterm delivery, and adverse effects.

The study observed that *Escherichia coli* was the most commonly detected pathogenic bacteria with 50%prevalence. The bacteriologic cure rates after the treatment was lower in one-day as compared to the seven-day regimen group with–10.5% as the cure rate difference (Fig 5 and 6). Significantly lower birth weight and

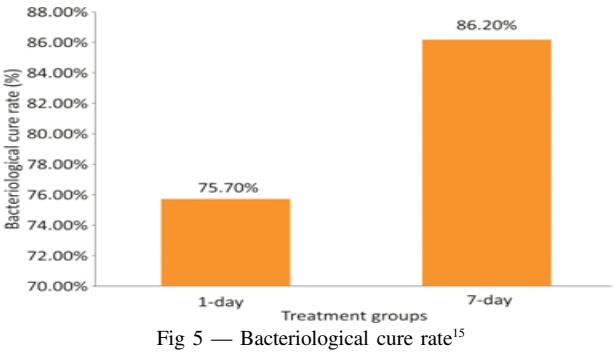

Fig 5 — Bacteriological cure rate[15]

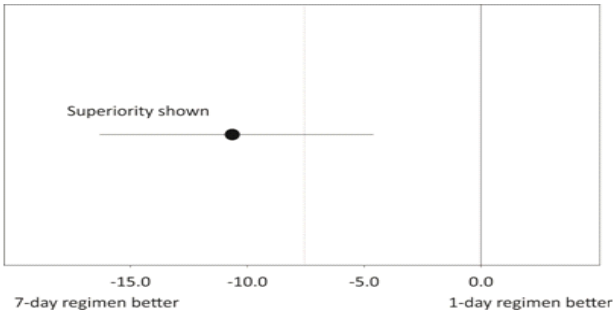

Fig 6 — Bacteriologic cure rate difference (%) with 1-day regimen compared with 7-day regimen[15]

gestational age was reported at delivery in the one-day regimen group. Fewer adverse effects were observed in the one-day regimen group.

The study results demonstrates that nitrofurantoin one-day regimen is significantly less effective as compared to the seven-day regimen. Thus, pregnant women with asymptomatic bacteriuria should receive the standard seven-day regimen.

- **Investigating the efficacy of low-dose nitrofurantoin for the management of urinary tract infections in the patients with spinal cord injury[16]**

A prospective study was conducted to evaluate the low-dose nitrofurantoin efficacy for the prevention of urinary tract infections (UTI) in the patients with spinal cord-injury.

The study enrolled 60 patients with spinal cord injury and were randomized to (Group I) receive 50 mg nitrofurantoin (in the form of encapsulate macro-crystals)

every 12 hours and Group II with no antibacterial treatment. Additionally all the patients received same level of catheter care. The urinalysis, sediment examination and culture test were performed urines in all the patients.

The study reported that all the patients presented with bacteriuria at least one time during the study period. But, significantly increase bacteriuria with a pathogenic organism followed by an increase in pyuria was observed in Group II as compared to group I.

Fourteen patients in Group 1 and 29 patients in Group 2 experienced a total of 35 weeks and 11 weeks of sterile urines, without pathogens or colonizers. Whereas, pseudomonas was isolated in 23 and 17patients from urines in the group I and II respectively.

From the results it is evident that, low dose nitrofurantoin therapy even with a history of previous urinary infections is effective in preventing repeated pathogenic organisms invasion of the bladder urine in spinal cord injured patients. Additionally, low dose-nitrofurantoin prove to be non-toxic and free from side effects with no reported emergence of bacterial resistant.

- **Evaluating the safety and efficacy of nitrofurantoin and fosfomycin long-term use in the treatment of recurrent urinary tract infections in type-2 diabetes women[17]**

Management of recurrent urinary tract infections in the type-2 diabetes patients is still an unsettled issue. Thus, the study was done with an aim to compare the safety and efficacy of nitrofurantoin and fosfomycin for the long-term treatment of recurrent uncomplicated lower urinary tract infections (uUTIs).

The study enrolled 50 type 2 diabetic women suffering from uUTIs with at least three recurrent episodes. The subjects were randomized to receive 3.0 g fosfomycin (FT) and 100 mg nitrofurantoin (NF) with a 6-months of follow-up. During the follow-up, urine bacteriology and complete blood cell count were performed, aminotransferase levels and renal function parameters were assessed.

At 3months, 96% in NF group and 92% in FT group patients were without the signs of UTI but the difference was not statistically significant (Fig 7). No significant differences was observed in the percentage of patients with UTIs at 3 and 6 months of long-term treatment between the study groups (Fig 7 and 8).

From the study results, it is evident that nitrofurantoin and fosfomycin are effective for the treatment and prevention of recurrent uUTIs in type 2 diabetes women and can be continued for several months.

- **Assessing the nitrofurantoinefficacy for the treatment of lower urinary tract infection (UTI) caused by extended-spectrumb-lactamase (ESBL)- producing *E.coli* in children[18]**

One of the commonest infections in children is urinary tract infections (UTI). The prevalence of acute cystitis due to ESBL- producing *Escherichia coli (E.coli)* is increasing

Table 3 — *Incidence of urinary infections*[16]

Incidents of UTI	Group 1 NF* (31 Patients)	Group 2 no NF (29 Patients)
0	24 (74%)	4 (14%)
1	7	6
2	1	9
3	0	4
4	0	6
Total UTIs	9 (8 patients)	60 (25 Patients)

*NF – nitrofurantoin 50 mg q. 12 h.

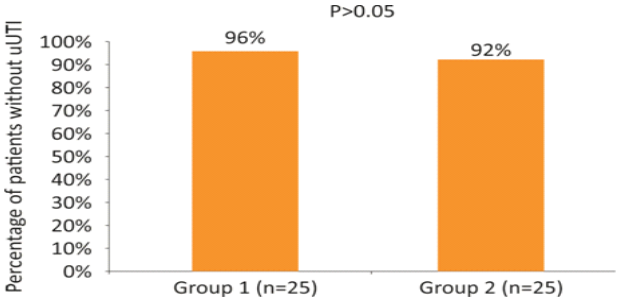

Fig 7 — Percentage of patients per study group without the signs of urinary tract infection at 3 months of long-term antibacterial treatment[17]

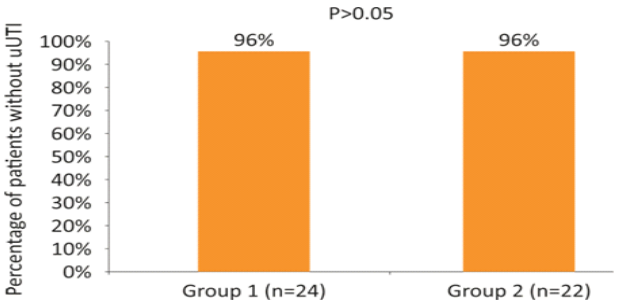

Fig 8 — Percentage of patients per study group without the signs of urinary tract infection at 6 months of long-term antibacterial treatment[17]

Table 4 — *Response rates and laboratory parameters after nitrofurantoin therapy*

Parameters	Observation
Clinical response (loss of symptoms) (%)	100%
Inflammatory response (loss of pyuria) (%)	98%
Bacteriological response (sterilization of urine cultures after treatment) (%)	98%
Non-scarring on renal Tc-99 m DMSA (%)	96%
Serum creatinine levels (mg/dL)	0.42 ± 0.19

in the children. The prospective study was conducted to assess the clinical and microbiological efficacy of nitrofurantoin for the lower UTI treatment caused by ESBL-producing *E.coli.*

Fifty children with lower UTI due to ESBL-producing *E.coli* were enrolled for the study. Patients who are susceptible to nitrofurantoin were given oral nitrofurantoin treatment for 10 days. Patients were assessed for

symptoms, clinical and laboratory parameters at 3-4 days after the end of treatment. 1-3 months after the end of treatment, renal scintigraphy was performed.

The study observed that 49 of 50 patients shows bacteriological response (98%). Normal serum creatinine levels was reported for all the patients. No symptoms and significant side effects were reported in any of the patients after the treatment. Renal scintigraphy, 1-3 months after completion of treatment, reported non-scarring in 48 of 50 of the patients (96%).

The study demonstrates that UTIs due to ESBL-producing *E. coli* are a serious problem which is due to the bacteria's multi-drug antibiotic resistant pattern. The results suggest that nitrofurantoin would be better alternative in the pediatric patients with UTIs caused by ESBL-producing *E. coli.*

RECOMMENDATIONS:

Recommendations	
IDSA (Infectious Diseases Society of America)[19]	Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for 5 days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage and efficacy comparable to 3 days of trimethoprim-sulfamethoxazole.
SIGN[20]	• Treat non-pregnant women of any age with symptoms or signs of acute LUTI with a three day course of nitrofurantoin. • Treat non-pregnant women of any age with symptoms or signs of acute LUTI with a three day course of nitrofurantoin.
NICE[21]	• As a first-line therapy in recurrent UTI: # for ≥16 years- 100 mg single dose when exposed to a trigger or 50 to 100 mg at night of nitrofurantoin (if eGFR e"45 ml/minute) # for <16 years- 3 months to 11 years, 1 mg/kg at night; 12 to 15 years, 50 to 100 mg at night (if eGFR ≥45 ml/minute)

Summary:

Nitrofurantoin is a unique antibiotic which is effective against both gram-positive and gram-negative organisms associated with UTIs. As compared to other drugs nitrofurantoin is relatively safer. The macro-crystalline formulations of nitrofurantoin has several advantages over micro-crystalline one with fewer side effects. It is commonly used for LUTI, used for recurrent UTI, catheter associated UTI, acute uncomplicated cystitis in women, multi drug-resistant strains UTI and in the UTI with special population including in pregnancy and diabetes.Nitrofurantoin was safe and effective in the treatment of LUTI with lower risk of developing resistance.

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