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NITROFURANTOIN – Potential drug, to become empirical therapy against urinary tract infections once again.

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Abstract-
Background – *Majority of the uropathogens being isolated these days, are found to be multidrug resistant.* ***Aim –*** *The aim of this study was to assess the sensitivity pattern for various bacteria isolated and compare it with that of nitrofurantoin.* ***Materials and methods –*** *urine samples from patients clinically diagnosed to have UTI were submitted in sterile, wide mouthed, screw capped universal container. 100 isolates from these samples were taken up for further evaluation for sensitivity pattern.* ***Result –*** *Nitrofurantoin was sensitive against 66.67% K.pneumoniae isolates, 79.48% E.coli, 100% Enterobacter spp., 50% Citrobacter spp., 75% Enterococcus spp., 100% S.aureus and 100% CONS.* ***Conclusions –*** *Nitrofurantoin has the potential to occupy the position of empirical drug once again, as it shows high sensitivity rates, is an oral drug, is easily available and is very cost effective.*

Keywords – *UTI, resistance, Nitrofurantoin, empirical drug.*

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I. Introduction

Urinary tract infections (UTI) is defined as a disease caused by microbial invasion of the urinary tract extending between the renal cortex of the kidney and the urethral meatus. It can be classified into lower UTI and upper UTI on the basis of anatomical sites which are affected by the disease. UTI can again be of two types depending on the source of infection. These are namely, Community acquired and Hospital acquired UTI.

UTIs accounts for second most common community acquired infections after respiratory tract infections. Among hospital acquired infections (HAIs), UTIs are the most common ones counting upto 35% of total HAIs. Such HAIs, are also sometimes known as DAIs (Device associated infections) because they are associated with catheterization in hospitalized patients. The term given to UTIs in catheterized patients is CAUTI (catheter associated urinary tract infections). CAUTI is said to happen when catheter has been placed for more than 2 days.

Majority of such UTIs are caused due to Escherichia coli. Other causative organisms known are Klebsiella pneumoniae, Enterobacter spp., Citrobacter spp., Pseudomonas spp., Proteus spp., Staphylococcus aureus, Enterococcus spp., Staphylococcus saprophyticus etc.

Nitrofurantoin is a synthetic derivative of imidazolidinedione. It inhibits synthesis of bacterial DNA, RNA and cell wall proteins. Its an oral antibiotic used either to treat acute uncomplicated urinary tract infections, as chronic prophylaxis against recurrent infections or as prophylaxis in catheterized patients. Inspite of the good range of activity, nitrofurantoin could never successfully maintain its position as empirical therapy for UTIs, probably due to the lesser compliance of patients and more number of side effects it produces. It is known to be one of the most common cause of drug induced liver disease. But at the same time, if prescribed judiciously, it bears the potential to become the empirical treatment for UTIs especially in scenarios where a huge proportion of uropathogens isolated these days are multidrug resistant.

II. Aim

The sensitivity pattern of commonly isolated pathogens in a locality keep on constantly changing depending upon the antibiotics being used against them at the present times and in the recent past. Through many studies it has been proven that bacteria become susceptible to those antibiotics which do not appear in regular prescriptions at present. Nitrofurantoin is one such drug against uropathogens. Hence, the aim of this study is to evaluate the resistance pattern of the uropathogens isolated locally and at the same time, to quantify the susceptibility to the old drug Nitrofurantoin.

III. Materials And Methods

This study was conducted in the Department of Microbiology, Phulo Jhano Medical College and Hospital, Jharkhand between February, 2020 to December, 2020. Urine samples coming from both patients

attending OPDs for UTI like symptoms as well as those admitted in IPDs were taken for this study. All the non-catheterized patients were explained about the correct way to collect clean catch midstream urine. The staffs attending the catheterized patients were explained on how to collect urine samples from the catheter tube aseptically after having priorly clamped it for half an hour.

All the samples were subjected to direct microscopy for observing presence or absence of pus cells, bacteria, RBCs, epithelial cells, casts and crystals. The samples, irrespective of the observation in direct microscopy, were inoculated onto CLED media for semiquantitative culture. Nichrome wire loop of 0.001µl capacity was used to pick the samples for inoculation. The plates were incubated aerobically at 37˚C for 18-24 hrs. Later, the plates were observed for growth, its colony morphology which was followed by gram's staining and biochemical tests for the same.

For all the organisms which grew as pure culture, antibiotic susceptibility testing was done by Kirby Bauer Disk Diffusion technique. The antibiotic discs to be tested were chosen according to the CLSI guidelines. The Hi Media antibiotic discs used were Ampicillin (10µg), Amikacin (30µg) , Nitrofurantoin (300 µg) , Piperacillin+Tazobactum (100/10µg) , Imipenem (10µg) , Nalidixic acid (30 µg), Levofloxacin (5µg) , Tetracycline (30 µg) , Cefotaxime (30µg), Amoxyclave (20/10 µg), Azithromycin (15 µg), Cotrimoxazole (T:S-1.25/23.75 µg), Erythromycin(15 µg), Clindamycin (2 µg), Linezolid (30 µg).

IV. Result

A total of 100 isolates were included in this study. The plates which showed either no growth or mixed growth were excluded. The organisms isolated were Klebsiella pneumonia (42%), Escherichia coli (39%), Pseudomonas spp. (6%), Enterococcus spp. (4%), Staphylococcus aureus (3%), Enterobacter spp. (2%), Citrobacter spp. (2%), CONS (1%) and Proteus spp. (1%). Out of the 42 isolates of K.pneumoniae, 71.4% were sensitive to Imipenem, 69.04% to Amikacin and 66.67% to Nitrofurantoin.

Table 1: Percentage isolates of K.pneumoniae which were susceptible, intermediate and resistant to the antibiotics.

Antibiotic discs	% susceptible	% intermediate	% resistant
Nitrofurantoin	66.67	21.4	11.9
Imipenem	71.4	2.38	26.19
Amikacin	69.04	7.14	23.8
Levofloxacin	47.61	11.9	40.47
Nalidixic acid	35.71	16.67	47.61
Cotrimoxazole	14.28	11.9	73.8
Azithromycin	52.38	0	47.61
Piperacillin-tazobactam	50	16.67	33.33
Amoxyclave	23.8	14.28	61.9
Cefotaxime	11.9	0	88.09
Tetracycline	73.8	0	26.19
Ampicillin	16.67	0	83.33

Graph 1: Bar graph depicting sensitivity pattern of K.pneumoniae isolates.

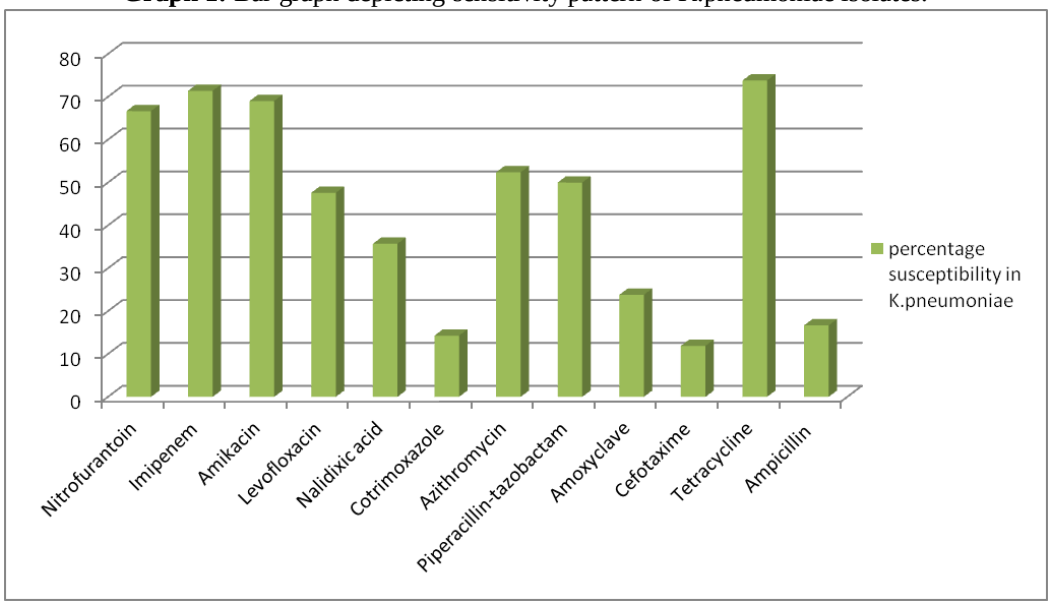


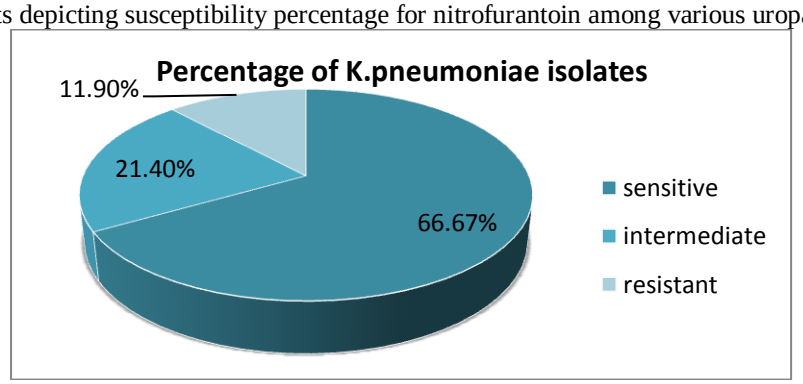
Table 2: Percentage isolates of E.coli which were susceptible, intermediate and resistant to the antibiotics.

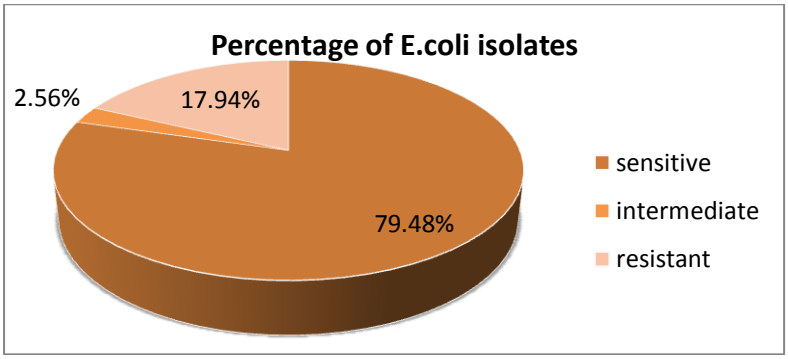
Antibiotic discs	% susceptible	% intermediate	% resistant
Nitrofurantoin	79.48	2.56	17.94
Imipenem	71.79	7.69	20.51
Amikacin	64.1	10.25	53.84
Levofloxacin	23.07	0	76.9
Nalidixic acid	12.82	0	87.17
Cotrimoxazole	10.25	12.82	76.9
Azithromycin	25.64	5.12	69.23
Piperacillin-tazobactam	51.28	23.07	25.64
Amoxyclave	10.25	23.07	61.9
Cefotaxime	7.69	10.25	82.05
Tetracycline	48.71	0	51.28
Ampicillin	7.69	0	92.3

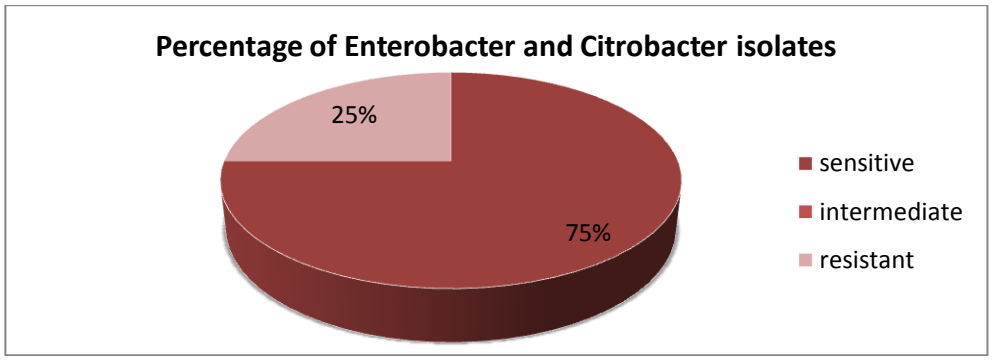
Table 3: Percentage of Gram positive isolates (S.aureus, Enterococcus spp., CONS) which were susceptible, intermediate and resistant to the antibiotics.

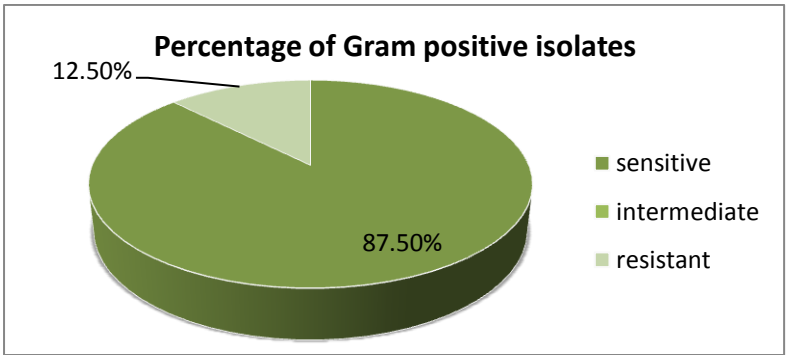
Antibiotic discs	% susceptible	% intermediate	% resistant
Nitrofurantoin	87.5	0	12.5
Amikacin	87.5	0	12.5
Levofloxacin	25	0	75
Nalidixic acid	0	12.5	87.5
Cotrimoxazole	50	0	50
Erythromycin	37.5	37.5	25
Amoxyclave	50	0	50
Ampicillin	25	12.5	62.5
Cefotaxime	37.5	0	62.5
Tetracycline	37.5	12.5	50
Clindamycin	75	0	25
Linezolid	100	0	0

Graph 2: Pie charts depicting susceptibility percentage for nitrofurantoin among various uropathogens isolated.









Overall, out of 93 isolates, 69 were susceptible to nitrofurantoin (Since, Nitrofurantoin is not recommended for Pseudomonas spp. and Proteus spp., these isolates were excluded from the calculation). Hence, for this study, the overall sensitivity for Nitrofurantoin was 74.19%, which is a considerably high percentage.

V. Discussion

In this study, the sensitivity for some injectables were the highest but injectables are not feasible in all scenarios. Hence, nitrofurantoin becomes a better option as it an oral drug with high sensitivity percentage and very cost effective too.

Saurabh et al (2017), found that nitrofurantoin susceptibility for E.coli was 72.3%, Klebsiella 30.6%, Enterococcus 69.71%, S.aureus 85.71%, Enterobacter 60% and CONS 100%. In the study done by Mariraj et al (2016), the overall susceptibility for uropathogens was 80-90% and Rajesh et al (2010), found that E.coli was 82%, Klebsiella spp.92%, Enterococcus 0% sensitive to nitrofurantoin.

Prevention is always better than cure. As far as HAIs are concerned, a set of infection control practices can be used to prevent them. Those are namely Standard (routine) precautions and Specific (transmission based) precautions.

Nowadays, hospitals follow bundle care approach for the prevention of DAIs. Bundle care for urinary catheter includes insertion bundle and maintenance bundle. The former constitutes steps like insertion of catheter only when appropriate indication is present, use of appropriate size catheter, use of only sterile items, insertion by non-touch technique with strict asepsis, use of a closed drainage and use of plaster-tube-plaster technique for properly securing the catheter in place. Maintenance bundle constitutes steps like daily catheter care; assuring that catheter is properly secured all the time and closed drainage system is maintained; drainage bag should always be above floor level and below bladder level; while decanting urine from bag, there should be change of gloves between patients, there should be use of separate jugs for each bag, alcohol swabs should be used to disinfect the outlet; and catheters should be daily assessed about readiness for removal.

VI. Conclusion

Inspite of widespread resistance against fluoroquinolones, this drug manages to secure its place as an empirical drug for UTIs. This leads to incomplete killing of the uropathogens which further result in chronic UTIs and also increases the resistance among bacteria. Hence, it will be wise to replace such a drug with one which shows better resistogram. In this study, we see that Nitrofurantoin has a considerably high sensitivity percentage. Therefore, if judiciously used and followed up for side effects, nitrofurantoin is a good empirical drug option in UTI. Further, antimicrobial surveillance from time to time would help detect any local change in the sensitivity pattern.

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