

# Prospective study to compare antibiosis versus the association of N-acetylcysteine, D-mannose and *Morinda citrifolia* fruit extract in preventing urinary tract infections in patients submitted to urodynamic investigation

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## Summary

**Background:** The abuse of antimicrobial drugs has increased the resistance of microorganisms to treatments, thus to make urinary tract infections (UTIs) more difficult to eradicate. Among natural substances used to prevent UTI, literature has provided preliminary data of the beneficial effects of D-mannose, N-acetylcysteine, and *Morinda citrifolia* fruit extract, due to their complementary mechanism of action which contributes respectively to limit bacteria adhesion to the urothelium, to destroy bacterial pathogenic biofilm, and to the anti-inflammatory and analgesic activity. The purpose of this study was to compare the administration of an association of D-mannose, N-acetylcysteine (NAC) and *Morinda citrifolia* extract versus antibiotic therapy in the prophylaxis of UTIs potentially associated with urological mini-invasive diagnostics procedures, in clinical model of the urodynamic investigation.

**Methods:** 80 patients eligible for urodynamic examination, 42 men and 38 women, have been prospectively enrolled in the study and randomised in two groups (A and B) of 40 individuals. Patients of group A followed antibiotic therapy with Prulifloxacin, by mouth 400 mg/day for 5 days, while patients of the group B followed the association of mannose and NAC therapy, two vials/day for 7 days. Ten days after the urodynamic study, the patients were submitted to urine examination and urine culture.

**Results:** The follow up assessment didn't show statistical significant difference between the two groups regarding the incidence of UTI.

**Conclusions:** The association of mannose and NAC therapy resulted similar to the antibiotic therapy in preventing UTIs in patients submitted to urodynamic examination. This result leads to consider the possible use of these nutraceutical agents as a good alternative in the prophylaxis of the UTI afterwards urological procedures in urodynamics.

**KEY WORDS:** Urinary Tract Infection (UTI); D-mannose - N-acetylcysteine (NAC); Urodynamic; Biofilm.

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Competing interests

Zanello PierPaolo: Consultant: Deakos.

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## INTRODUCTION

Urinary tract infections (UTIs) are defined as the presence and the proliferation of bacteria which are pathogens in one or more parts of the urinary tract with subsequent invasion of tissue and the onset of symptoms. UTIs represent a great problem for the public health systems, because they are responsible for high morbidity and are also one of the main causes of antibiotic prescriptions associated to an increased resistance to them (1).

In Europe UTIs represent the second cause of bacterial infection, after the respiratory, and are the most frequent form of nosocomial infections, associated mostly to the bladder catheterism (2, 3). Furthermore, the high volume of antibiotics used to face UTIs determines high costs for the sanitary systems and their abuse has significantly contributed to the development of resistance mechanisms of the germs to these drugs (4). Females are usually more exposed to this pathologic condition due to anatomical factors. However, after the age of 50, the risk of UTI increases also for men because of obstructive problems due to the benign prostatic hypertrophy (Table 1).

Some other factors may contribute to increase the risk of developing UTI, and they should not be underestimated, such as intrauterine contraceptives (spiral), pregnancy (because it causes urinary stasis), menopausal status, anatomical and endocrine disruptors, constipation, wrong behavioural habits, various types of urinary catheterisms (ureteral stent, nephrostomy, intermittent or indwelling bladder catheterization). The Annual Epidemiological report of the European Centre for Disease Prevention and Control (ECDC) published in April 2015, reported that pathogenic agent which is responsible of most UTIs (about 70%) is *Escherichia coli*, a bacteria of faecal origin which belongs to the gram-negative (5). *E. coli* is an emerging problem also regarding community acquired UTI either in pediatric population either in the adult and elderly subjects (4). Particularly, subjects with severe chronic urinary dysfunc-

**Table 1.**  
Risk factors and prevalence of UTIs according to the age and sex.

Age	Women		Men	
	Prevalence (%)	Risk factors	Prevalence (%)	Risk factors
< 1	1	Functional or anatomic alterations of the urinary tract; Incomplete immune system	1	Functional or anatomic alterations of the urinary tract; Incomplete immune system
1-5	4-5	Vesicoureteral reflux; congenital alterations	0.5	Congenital alterations
6-15	4-5	Vesicoureteral reflux	0.5	No
16-35	20	Sexual relations; Diaphragm/spiral and spermicide; Pregnancy	0.5	Sexual relations
36-65	35	Estrogens deficit (post-menopausal); gynaecological surgery; neurological disorders; vesicoureteral reflux; vaginal prolapse; instrumentations; dismetabolic disease; lithiasis	20	Vesicoureteral reflux; benign prostatic hyperplasia; stenosis; neurological disorders; surgery; instrumentations; dismetabolic disease; lithiasis
> 65	30	Idem + incontinence, bladder catheterism; antimicrobial therapy	35	Idem + incontinence, bladder catheterism; antimicrobial therapy

tions secondary to neuropathies and people recovered in intensive care units are exposed to UTIs (6, 7).

For these reasons, a better understanding of mechanisms which induce the germs' resistance to antibiotics is needed, such as improvement of the strategies to prevent infections and their recurrences, with the aim to limit use of antibiotics in the clinical practice.

In the urinary tract, the interaction between pathogen bacteria and the epithelium is mediated by various factors located on the bacteria cell or secreted by the same. In fact, adhesion of bacteria is a complex process, depending on the presence of certain fimbrial/pili structures that allow a specific interaction of the microbe with certain host cell receptors (8). These structures are represented by proteins, called adhesins, that allow the specific and selective bacterial adhesion. Specifically, two different types of pili are distinguished: 1) mannose - sensitive, pili or fimbria type I; 2) mannose - resistant, pili or fimbria type II.

The type I are the main responsible factor for the colonization and invasion of the lower urinary tract due to the adhesion at urothelium cells level (8). However, another feature of the pathogen bacteria is the ability to produce, under favourable conditions, a large quantity of a particular capsular material: the biofilm (9, 10). Pathogenic biofilms represent the still neglected etiology of recurrences. Biofilms are polymicrobial structured communities, composed by 15% of bacteria and/or fungi and 85% of a self-produced mucopolysaccharides polymeric matrix. On biological surface, biofilms can be intra- or extracellular, in the bladder or on mucous surface respectively, but they can also adhere to an inert structure, such as catheter or other medical device. Pathogens live in a quiescent state in the deep layers of biofilm as "persister cells", phenotypically resistant to antibiotics and host defences and ready to re-attack the host. Biofilm has an important role in UTIs pathogenesis, especially when intracellular, established inside bladder cells, because it doesn't allow to pharmacological treatments and to the autoimmune system to reach bacteria efficiently. Furthermore, biofilm have a complex and ingenious architecture that mimics a primitive circulatory system, with particular structures called "water channels" and "pore", allow both the distribution of nutrient,

signalling molecule, for the removal of toxic substances too (10). It also allows the transition of genes, thanks to the physical proximity of bacterial cells, contributing to resistant infections and drugs- resistance (11).

Particularly considering the risk to induce drugs resistance by germs, the possible side effects, such as intestinal dysbiosis, the use of antibiotics should be very careful. Aim of this research is to find an alternative natural approach instead of antibiotics prophylaxis to prevent UTIs, such as in mini-invasive diagnostic urodynamics procedures. In fact, a large use of antibiotics is applied to prevent infections, especially in men, potentially related to various diagnostic invasive urological examinations. Considering the pathophysiologic mechanisms that mostly contribute to the bacteria adhesion, to prevent the attachment and pathologic growth of bacteria and to promote the degradation of biofilm, must be considered as one of the main strategies to reduce the risk of UTIs.

An alternative to the antibiotic prophylaxis, in the prevention of UTIs which can arise after urological procedures, could be the use of natural substances, especially when the microbial load is still low. One of these substances is *D-mannose*, an inert monosaccharide which is physiologically present in the human body (12-14). After assumption, *D-mannose* is sparsely metabolized, and mostly removed through the urine. The mechanism of action is represented by the inhibition of bacterial adhesion to the urothelium, interfering with fimbrial adhesins type I - Mannose - sensitive.

*D-mannose* plays an important role also in other functions such as the ability to regenerate glycosaminoglycans (GAGs) of bladder and mucosal surface, after injury, and to detach bacteria already linked at the urothelium (12-14). Its beneficial effects in reducing UTI and complementary and integrative therapy for lower urinary tract inflammatory diseases have been shown by various studies (15-17). However, *D-mannose* is ineffective against the pathogens inside biofilm thus to induce the need of further action to better prevent the persistence and recurrence of UTI, and the bacterial resistance. Some evidence has already been provided about the ability of *N-acetylcysteine* on reducing bacterial biofilm either in vitro and in vivo studies (18, 19). These investigations showed a clinical benefit due to an high ability to dis-

solve the ripe biofilm matrix. Therefore, it has already been reported that *N-acetylcysteine* could be useful in the treatment of UTI, also caused by *E. coli*, due to its inhibitory effect on both bacterial growth and biofilm formation (20).

In recent years, the growing interest in phytotherapeutic remedies has focused a particular interest also to *Morinda citrifolia* fruit, a native plant of South - East Asia, Polynesia and Hawaii. The demonstrated range of therapeutic effects of *Morinda citrifolia* fruit is attributable to the richness of its chemical components: *Xeronine*, *Proxeronine*, *Scopoletin*, *Octoanoic acid*, *potassium*, *vitamin C*, *terpenoids*, *alkaloids*, *anthraquinones*, *linoleic acid*, *Alizarin*, *amino acids*, *Acubine*, *L-asperuloside*, *caprylic acid*, *ursolic acid*, *rutin*, *carotene*, *vitamin A* (21). The dry fruit extract is commonly used in various nutritional supplements products for its antibacterial, anti-inflammatory, analgesic and immunomodulatory activity, suggesting a great role also in recurrent UTIs prevention.

For all the overmentioned considerations, it appeared of interest to design a study to evaluate the efficacy of a combination of *D-mannose*, *N-acetylcysteine* and *Morinda citrifolia* extract on UTIs after urodynamic procedures.

Aim of this clinical study was to compare assumption of a phytoterapeutic product composed by *D-mannose*, *N-acetylcysteine* and *Morinda citrifolia* extract (registered as *Ausilium NAC*<sup>®</sup> by *Deakos s.r.l. Corso Nazionale, 169 - La Spezia*), versus the antibiotic prophylaxis with fluoroquinolones, in preventing UTIs potentially related to mini-invasive urological diagnostic procedures. To achieve this goal, the urodynamic examination represented the experimental clinical model.

## MATERIALS AND METHODS

The clinical study has been conducted at the *University of Rome, La Sapienza, Unit of Urology, ICOT Hospital, Latina*. From February to September 2015, 80 patients have been subjected to the urodynamic examination. Patients have been chosen random in a cohort study including 42 men and 38 women. At the preliminary urologic consultation, all patients were submitted to history, physical examination including digital rectal examination in men and vaginal exploration in women. The day for the urodynamic investigation was planned and all the subjects were invited to present urine examination and urine culture 7 days before the test. Patients with pathological findings at urine examination (presence of nitrites and pathological number of leukocytes in the urine sediment) and/or with positive urine culture suggestive for UTI (defined by > 10<sup>5</sup> colony-forming units/ML) were invited to assume antibiotics basing on antibiogram and were excluded from this protocol. All the other patients with negative urine examination and negative urine culture were considered and accepted to be screened for the study, after they have signed an informed consent.

Inclusion criteria were considered: legal age (18 years in Italy) and ability to understand and sign the informed consent.

Exclusion criteria were represented by: history of recent hematuria (within 3 months), presence of indwelling catheter or nephrostomy or suprapubic catheter or ureteral stent, recent urological, gynaecological or pelvic

surgery (within 3 months), neoplastic disease, evidence or suspicious of fistula, diagnosis of interstitial cystitis, pathological findings at physical examination (e.g., digital rectal exploration suspicious for prostate cancer or suggestive for prostatitis). All patients satisfying inclusion criteria were then enrolled. Therefore, the 80 patients considered for the protocol came from a preliminary population of 134 individuals attending our outpatient office. Following those criteria, a randomized procedure was used for the random allocation of the enrolled patients into two groups of 40 in equal proportions to ensure a uniform allocation ratio (1:1). A specific protocol has been developed for each group:

**Group A:** traditional treatment with antibiotics *Prulifloxacin* by mouth, 400 mg/day, for 5 days starting from the day before the procedure. *Prulifloxacin* is the antibiotic suggested by the service for the prevention and treatment of the infective diseases of the hospital; thus it represents the recommended antibiotic for urological practice in our institution.

**Group B:** oral administration of two vials/day of *Ausilium NAC*<sup>®</sup> for 7 days starting from the day of the examination. Each vial contain *D-mannose* 500 mg, *N-acetylcysteine* 100 mg and *Morinda citrifolia* fruit extract 300 mg, an anti-inflammatory, immunostimulant and analgesic phytoterapeutic remedy.

After 10 days from urodynamic test, a second laboratory assessment based on urine examination and urine culture was performed in all patients. Results were observed and submitted to statistical analysis, which was performed using the S-PSS 20.0 software. At beginning, a careful analysis was conducted to evaluate the statistical homogeneity among the two groups (either *prulifloxacin*, or *Ausilium NAC*<sup>®</sup>) according to the demographic data and comorbidities. Then, patients were compared according to their group allocation and analysis of variance was used to find the significance of study parameters among the groups of patients. Fisher's exact test, Mann-Whitney, and 95% confidence intervals were used as appropriate. Two-tailed p value of less than 0.05 was considered as statistically significant. The local Ethical Committee, as prescribed by law, was informed of this observational investigation before starting the protocol. Schematic overview of experimental design is represented in Figure 1.

## RESULTS

The results obtained from the anamnestic assessments between the two groups did not show significant difference in relation to the age, sex, body mass index, menopausal status, co-morbidities and pharmacotherapy (p value > 0.05). The population enrolled in the study was stratified according to the age, benign prostatic hyperplasia (BPH), menopausal status, different birthing modalities, hypertension/heart diseases, diabetes, dysthyroidism, gynaecological and urological surgery or other pathologies, called "Other" (such as osteoporosis, dyslipidaemia, depressive illness, etc.) as indicated in Table 2. During the treatment, 5 patients spontaneously

**Table 2.**  
Clinical and demographic characteristics of the two experimental groups performed.

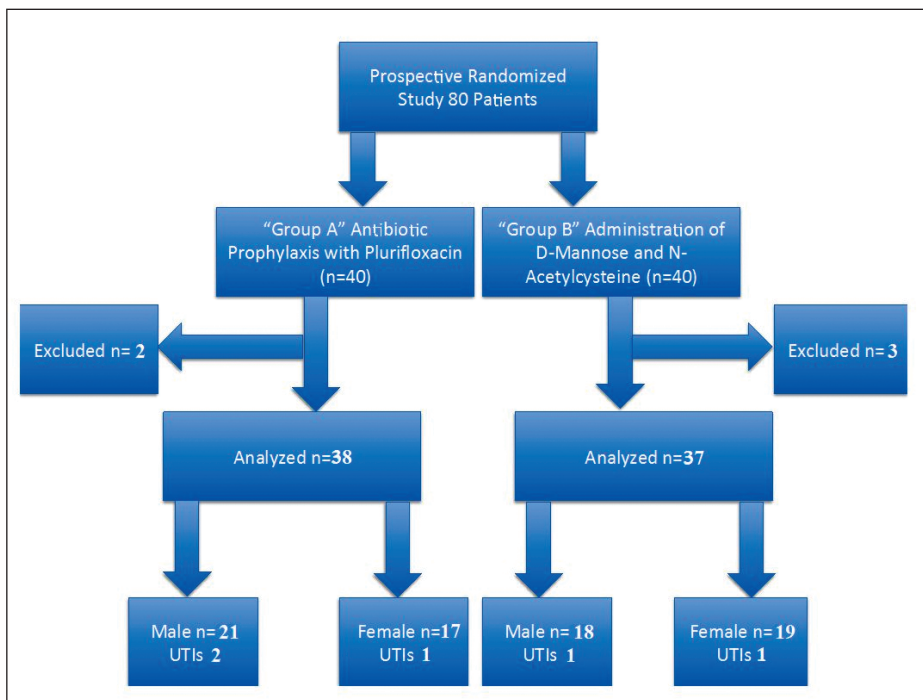
	Prulifloxacin			Ausilium NAC		
	Men	Women	Tot	Men	Women	Tot
Patients	n = 21	n = 17	n = 38	n = 18	n = 19	n = 37
Average age (± 95%)	65 (± 1.62)	56 (± 1.39)	65.4 (± 1.03)	64 (± 1.45)	54.42 (± 1.88)	65.4 (± 1.09)
Diabets	3	1	4	4	1	5
Menopausal status	/	12	12	/	11	11
B.P.H.*	15	/	15	12	/	12
Hypertension/heart disease	2	2	4	1	2	3
Dysthyroidism	1	1	2	/	1	1
Natural childbirth	/	3	3	/	4	4
Urological surgery	2	/	2	2	/	2
Uro-gynaecological surgery	/	3	3	/	5	5
Other	/	4	4	/	2	2

\* Benign Prostatic Hyperplasia.

abandoned the study due to scarce interest in continuing the protocol: 2 of them (both men) belonged to the Group A and 3 (1 man and 2 women) belonged to the Group B. Patients who left the study have been excluded

from the final evaluation. At the end of the study, 75 patients have been evaluated: 38 belonging to the group A and 37 belonging to the group B. They have been divided in other sub-groups according to sex: therefore,

**Figure 1.**  
Schematic overview of experimental design and results obtained in the study.



21/38 patients (55%) of group A and 18/37 patients (49%) of group B were men, while 17/38 patients (45%) of group A and 19/37 patients (51%) of group B were women. None patient reported side effects in both treatment groups. Schematic overview of experimental design and results obtained are represented in Figure 1. Obtained data denotes the same UTIs incidence in the two observed groups: 3/38 (7.89%) of the group A and 2/37 (5.4%) of the group B developed UTIs (p value = 0.671) (Table 3).

Considering the laboratory examinations performed at the follow-up visit, the results didn't show significant differences between the group A and B in terms of incidence of UTIs.

All the patients with UTIs were symptomatic; they were

**Table 3.**  
Percentage of UTIs occurred and germ isolated in the patients from group A, group B and sub-groups according to the sex.

Sex	Patients analyzed	Group A Prulifloxacin			Group B D-mannose and N-acetylcysteine		
		Men	Women	Tot	Men	Women	Tot
N° patients	75	21	17	38	18	19	37
% UTIs		9.5%	5.8%	7.89%	5.5%	5.2%	5.4%
Germ isolated		Escherichia coli 100%			Escherichia coli 100%		



treated with antibiotics basing on antibiogram, followed by further laboratory check after 15 days to ensure that UTI was cured.

The group A and B have been divided in other two subgroups in relation to the sex. Only 2/21 (9.5%) male patients and 1/17 (5.8%) female patients of the group A and 1/18 (5.5%) male patients and 1/19 (5.2%) female patients of the group B developed UTI after urodynamic procedures (p value = 0.946).

The results of this further division did not show particular predispositions to UTIs depending on the sex, antibiotics or nutraceuticals in urodynamic.

## DISCUSSION

The results of this study show that there was no significant difference regarding the incidence of UTIs between patients undergone treatment with fluorochinolones and those who assumed *Ausilium NAC*<sup>®</sup>.

The phytotherapeutic product combines *D-mannose*, able to reduce bacterial adhesion, *N-acetylcysteine*, a mucolytic molecule useful to destroy bacterial biofilms and *Morinda citrifolia* extract, with anti-inflammatory, immune stimulating and analgesic properties, in UTIs after urodynamics procedures. Therefore, assumption of *Ausilium NAC*<sup>®</sup>, two vials/day for one week provided the same protective effect in preventing UTIs respect to the prophylaxis with fluorochinolone *Prulifloxacin*. The two compared cohorts were substantially similar regarding comorbidities and clinical features, therefore this result has been not conditioned by clinical and demographical differences between the populations and it has to be specifically related to the action of treatments used. In case of invasive diagnostic urological procedure, which potentially carry the risk to induce UTIs, a very careful protocol is essential, such as sterility of instruments or correct prophylaxis post-intervention. As an additional strategy to reduce the risk of UTIs, instead of using antibiotics it should be preferable to use natural substances, basing on the evidence that these agents could provide the same protection especially when microbial load is still very low.

*In vitro* studies and preliminary clinical experiences demonstrated that *D-mannose* and *N-acetylcysteine* can provide a favourable effect in preventing UTIs (12, 15-20). The present study shows that *D-mannose*, *N-acetylcysteine* in association with *Morinda citrifolia* fruit extract in the formulation of *Ausilium NAC*<sup>®</sup>, like plurifloxacin, may provide a favourable effect in preventing UTI in case of mini-invasive diagnostic procedures which require bladder catheterism. An important advantage of nutraceutical agents is that a natural mechanism to prevent infections can avoid an unnecessary use of antibiotics, limiting the risk to develop germ resistance. Furthermore, even if it did not happen in our study, usually antibiotics are more responsible for dysbiosis and side effects if compared with natural substances. As a further consideration, patients accepted with pleasure to assume a nutraceutical agents rather than antibiotic prophylaxis to prevent UTIs.

The results obtained suggest to better explore, on larger case series, the advantage of this particular association of

nutraceuticals, whose action mechanisms are of particularly suitable interest in UTIs prevention.

The synergy between *D-mannose*, *N-acetylcysteine*, and *Morinda citrifolia* fruit extract, has suggested a great role in recurrent UTIs prevention (15-21).

A larger experience is needed, also in different type of populations, to amplify the outcomes shown in the present study. In fact, the limit of this study is represented by the single centre experience and the relatively limited number of subjects enrolled. However, the stratification of patients and the prospective design can partially balance these limits. Another criticism could be represented by the absence of a "non-treatment" group, but this was not allowed by the *Local Ethical Committee*. As a further consideration, it has to be underlined that, as various type of infections, also the risk of UTI may be strongly reduced by some other natural and non invasive prevention strategies. Behavioural aspects, reduction of comorbidities and attention to precipitating factors, are the most important. As a favourable consequence, a better management of antibiotics could limit the development of germ resistance which is becoming a serious health problem, particularly in hospitalized patients (8).

In fact, in the last years, many *Authors* reported the increased of UTI secondary to germs resistant to conventional antibiotic treatment (21). It is a common experience in real life management to face UTI sustained by germs which show multiple resistance, and one of the main factors that has led to multiple resistance is the indiscriminate use of antibiotics. Those circumstances require difficult strategies of treatment. Sometimes it is necessary the help of experts in contagious disease, a large dose of medicines and also hospitalization. Furthermore, in the last years considering the large availability of efficacious antibiotics, clinicians have made an excessive use and at the same time the research for new molecules has been decreased; therefore new classes of drugs suitable for the treatment of infections caused by multidrug-resistant germs are not currently available. For these reasons antibiosis prophylaxis must be restricted and replaced with alternative treatment whenever possible.

## CONCLUSIONS

This study proved that *Ausilium NAC*<sup>®</sup> is as efficient as the plurifloxacin in order to prevent UTIs potentially associated with urodynamic examination. This result should induce to consider that the assumption of nutraceutical substances without antibiotic effect can reduce the risk of UTIs, for less invasive urological procedures. The limited use of antibiotics in selected cases will contribute to reduce the development of antibacterial agents resistance. Further studies are requested to support the encouraging results of this experience, focusing the attention on a more careful use of antibiotics for UTIs prevention related to diagnostic procedures.

## AUTHORS' CONTRIBUTIONS

All *Authors* have contributed equally to the drafting of the manuscript. All *Authors* read and approved the final version of the manuscript.

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