CURRENT
THERAPEUTIC
RESEARCH®
VOL. 57, NO. 6, JUNE 1996

# PREVENTION OF RECURRENT URINARY TRACT INFECTIONS IN FEMALE CHILDREN

## OM-89 Immunotherapy Compared with Nitrofurantoin Prophylaxis in a Randomized Pilot Study

BERNHARD LETTGEN

*Universitätsklinikum Essen, Klinik für Kinder- und Jugendmedizin, Abteilung für Pädiatrische Nephrologie, Essen, Germany*

## ABSTRACT

**The aim of this randomized, controlled, open-label pilot study was to compare the efficacy and tolerability of long-term immunotherapy (OM-89) with that of nitrofuran chemotherapy (nitrofurantoin) to prevent recurrent urinary tract infections (UTIs) in female children. Of the 40 patients participating in this study (mean age, 6.5 years; range, 2 to 10 years), 22 were randomly assigned to group A (OM-89) and 18 to group B (nitrofurantoin). The study was carried out in three 6-month phases. In phase I (run-in) both groups were given nitrofurantoin 1 mg/kg/d (a standard prophylactic dose); in phase II, group A received one capsule per day of OM-89 (6 mg/d, active compound), and group B continued the nitrofurantoin treatment. Phase III was a follow-up phase without medication. The diagnosis of a bacterial UTI was based on clinical symptoms (dysuria) and positive urine culture (significant bacteriuria and pyuria). The results show that the oral OM-89 treatment elicits a highly significant decrease in UTIs compared with baseline (6-month prestudy data). The efficacy of the long-term administration of OM-89 in this study was comparable to that of nitrofurantoin during phase II (months 6 to 12) and phase III (months 12 to 18). OM-89 can be considered as an alternative to chemotherapeutic prophylaxis; OM-89 is well tolerated and effective in decreasing the incidence of UTIs in female children prone to recurrences.**

## INTRODUCTION

Girls, age 6 to 16 years, with bacteriuria are at a greater risk of developing symptomatic urinary tract infection (UTI) than the general population.[1,2] Children with undetected or inadequately treated UTIs are likely to have recurrent infections, chronic pyelonephritis, and, in adulthood, chronic renal failure requiring hemodialysis and renal transplantation.[1,3] A further complication is the continuing emergence of new antibiotic-resistant pathogens, which contributes to the high costs of patient care.[4]

Address correspondence to: Dr. Bernhard Lettgen, Klinik für Kinder- und Jugendmedizin, Universitätsklinikum, Essen, Hufelandstrasse 55, 45122 Essen, Germany.
*Received for publication on February 27, 1996.* Printed in the U.S.A.



0011-393X/96/$3.50

Leski[5] estimated that 50% of the young women who develop a UTI have a recurrence within 12 months. Etiologically, these reinfections are characterized by a greater adherence of intestinal bacteria to urethral and vaginal epithelia. The increased incidence of such infections also depends on local (within the urinary tract) immunocompetence.

Secretory immunoglobulin A (sIgA) and, to a lesser extent, immunoglobulin M are important mucosal defense mechanisms against colonization by bacteria, viruses, or fungi. It has been reported that levels of sIgA in the urine of female children and adults prone to recurrent UTIs are lower than levels found in uninfected controls,[6,7] thus reducing the mucosal defenses. Stimulating these defenses by elevating the production of sIgA could help reduce the frequency of recurrences. An alternative to antibiotic prophylaxis, which can have a negative effect on the immune system,[8] is the oral administration of immunomodulators. These compounds enhance the patient's own immune defenses against pathogens.

OM-89* is a lyophilized, bacterial proteinic extract obtained from the soluble components of combined alkalinized fractions of the gram-negative bacterium *Escherichia coli,* a pathogen commonly responsible for UTIs. Animal studies have shown that OM-89 prevents experimental infections and stimulates macrophages, phagocytosis, and activity of B lymphocytes and natural killer cells.[9–11] In addition, it increases the level of sIgA and opposes the immunosuppressive effect of certain antibiotics.[11,12] In vitro immunopharmacologic studies have shown that the extract enhances the production of interferon-gamma, tumor necrosis factor-alpha, and other cytokines,[9] as well as the metabolic and functional activities of lymphocytes and macrophages, which are important for host defenses.[10]

This pilot study was designed to compare the efficacy and tolerability of the long-term administration of OM-89 versus nitrofurantoin to prevent reinfection in female children with recurrent UTIs.

## PATIENTS AND METHODS

Forty female children with recurrent UTIs participated in this randomized, prospective, controlled study (mean age, 6.5 years; range, 2 to 10 years). Before enrollment, the patients underwent kidney and derivative urinary tract examination using ultrasonography. Children were enrolled in the study if they had had at least three episodes of acute UTIs within the last 12 months. The medical history was well known by the investigators and was documented in the case report form at entry into the study (prestudy data). The diagnosis of bacterial UTI (cystitis, urethritis, cysto-

* Marketed in Germany as Uro-Vaxom® (Sanofi-Winthrop Ltd., Munich) and Uro-Munal® (Deutsche OM Ltd., Friedrichsdorf).

Table I. Criteria used to diagnose urinary tract infections (UTIs).

| | Criteria | |
|---|---|---|
| | **Clinical** | **Laboratory** |
| Acute UTI (cystitis, urethritis, cystourethritis) | Dysuria, urgent, frequent micturition, suprapubic pain; no urinary symptoms in the 4 weeks before the episode | >10 WBCs/$mm^3$; $>10^{3-5}$ CFU/mL in 1 MSU culture |
| Acute pyelonephritis | Fever, chills, flank pain; other diagnoses excluded; no history or clinical evidence of urologic abnormalities | >10 WBCs/$mm^3$; $>10^4$ CFU/mL in 1 MSU culture |
| Asymptomatic bacteriuria | No urinary symptoms | >10 WBCs/$mm^3$; $>10^5$ CFU/mL in 2 consecutive MSU cultures >24 hours apart |
| Recurrent UTI (requiring antimicrobial prophylaxis) | At least 3 episodes of acute infection documented by culture in the last 12 months; no structural or functional abnormalities | >10 WBCs/$mm^3$; $>10^{3-5}$ CFU/mL in 1 MSU culture |

WBC = white blood cells; CFU = colony-forming units; MSU = midstream urine culture.

urethritis) was based on the clinical and laboratory criteria summarized in Table I (adapted from Rubin et al[13]). Patients with obstructive uropathy, chronic pyelonephritis, vesicoureteral reflux, or lithiasis were excluded. Patients with urinary incontinence were given ambulatory bladder training (ie, instructions to drink adequate amounts of liquid and to void frequently and completely at first urge) during the study. The study was approved by the local ethics committee. Parents gave their informed consent before entry.

Patients were randomly assigned to either group A (n = 22) or group B (n = 18). The study consisted of three 6-month phases, with regular control visits at entry and every 3 months thereafter. During phase I all patients were given nitrofurantoin* 1 mg/kg/d in the evening for 6 months. This dosing regimen is the amount required to protect the bladder overnight.

In phase II, group A was switched to OM-89, 6 mg/d lyophilized *E coli* fractions, given as one capsule daily in the morning on an empty stomach. Group B continued treatment with nitrofurantoin during phase II.

Both groups stopped prophylaxis during the final 6-month follow-up period (phase III), as shown in Figure 1. Compliance was assessed at each visit by checking the remaining medication in each patient's box and by questioning the parents.

The diagnosis of a UTI was based on the clinical signs associated with

* Trademark: Furadantin® (Röhm Pharma, Weiterstadt, Germany).

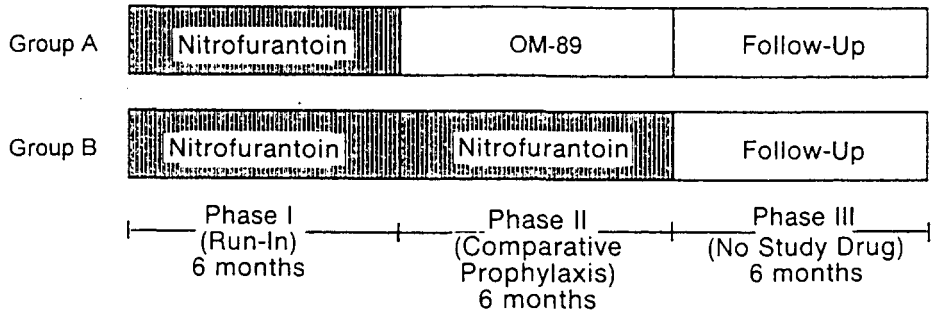


Figure 1. Treatment regimens for patients in group A (n = 22) and group B (n = 18) during the three phases of the 18-month study.

a positive urine culture. Detailed physical examinations, including urine sampling (clean-catch, midstream urine) and urinalysis, were performed at each visit (ie, at entry and after 3, 6, 9, 12, 15, and 18 months) or when acute events occurred. When an acute event occurred, the pathogen was identified microbiologically and its resistance determined to select the appropriate antibiotic treatment.

The efficacy of OM-89 in preventing reinfection was compared with that of standard prophylactic nitrofurantoin therapy used as active-control versus baseline (6-month prestudy data).

At each visit the investigator systematically questioned the patients regarding adverse events. All such events were recorded and subsequently assessed to determine whether they were associated with treatment.

### *Statistical Analysis*

Randomization to the two study groups was determined by the statistical center of the University Hospital, Essen, Germany. All randomized patients were statistically analyzed on an intent-to-treat (ITT) basis for efficacy and tolerability. A per-protocol or best-case approach was used to analyze the ITT patients. Patients with major (pyelonephritis) or minor (missing data) protocol violations were excluded from the per-protocol analysis. Patients with major protocol violations were excluded from the best-case approach; however, patients with only minor protocol violations were not excluded from best-case approach.

The nonparametric Wilcoxon's matched-pairs test was used to assess the frequency of UTIs within groups versus the 6-month prestudy period. The Mann-Whitney-Wilcoxon rank sum test was used for the comparison between groups. (The 95% confidence interval was used for both tests.)

All randomized patients who were correctly allocated, who met the inclusion criteria, and who had at least one control visit at entry were analyzed using the ITT principle. The results are expressed as mean ± SD.

## RESULTS

Of the 40 patients who participated in the trial, 22 were randomized to group A (mean age, 6.9 ± 2.8 years) and 18 to group B (mean age, 6.4 ± 2.9 years). These patients constituted the ITT population used to analyze the efficacy and tolerability of the study drugs. Both groups were comparable at entry with regard to age, height, body weight, and frequency of UTIs (Table II). During the study, 1 patient in group A attended the first visit at 3 months (phase I) but did not return for subsequent visits (lack of symptoms, minor protocol violation) (Table III). At the end of phase II, 1 patient receiving OM-89 contracted pyelonephritis (major protocol violation) necessitating antibiotic therapy. In group B, 4 patients did not attend the control visits (3 patients during phase II because they did not have UTI symptoms and 1 during phase III for unknown reasons). A fifth patient in group B developed pyelonephritis during phase III; antibiotic treatment was administered to this patient.

### *Efficacy*

Diagnosis of UTIs was determined on the basis of clinical and laboratory findings. Because 22% of patients (4 of 18) in group B were eliminated from the study during phase III for minor protocol violations (missing data) versus 4.5% of patients (1 of 22) in group A, a best-case approach was used to compensate for this loss. Thus the number and frequency of UTIs in both groups were analyzed using either the per-protocol or best-case approach on an ITT basis. When the per-protocol approach was used, only valid cases (those without major or minor protocol violations) were included. The best-case approach excluded patients with major protocol violations; those with only minor protocol violations were included in the best-case approach. In either case, the number and frequency of UTIs in the patients in group A compared with group B were not significantly different during any phase of the study (Figure 2).

During phase I (the nitrofurantoin run-in phase), one patient in each

Table II. Patient characteristics.

| | Group A (n = 22) | Group B (n = 18) |
|---|---|---|
| Age (y) | 6.9 ± 2.8 | 6.4 ± 2.9 |
| Height (cm) | 123.5 ± 16.4 | 118.7 ± 18.1 |
| Body weight (kg) | 26.6 ± 9.2 | 22.8 ± 6.9 |
| ESR (mm/h) | 0.4 ± 0.5 | 0.2 ± 0.4 |
| No. of UTIs during the last year | 3.8 ± 1.1 | 3.9 ± 1.0 |

ESR = erythrocyte sedimentation rate; UTI = urinary tract infection.

Table III. The number of patients available for statistical analysis during the 18-month study and the number of patients excluded and the reasons for exclusion.

| | Group A | | Group B | |
|---|---|---|---|---|
| Month | No. of Patients | No. of Exclusions | No. of Patients | No. of Exclusions |
| Baseline | 22 | 0 | 18 | 0 |
| Phase I | | | | |
| 3 Months | 21 | 1 (did not attend control visits) | 18 | 0 |
| 6 Months | 21 | 0 | 18 | 0 |
| Phase II | | | | |
| 9 Months | 21 | 0 | 16 | 2 (did not attend control visits) |
| 12 Months | 20 | 1 (pyelonephritis) | 15 | 1 (did not attend control visits) |
| Phase III | | | | |
| 15 Months | 20 | 0 | 14 | 1 (did not attend control visits) |
| 18 Months | 20 | 0 | 13 | 1 (pyelonephritis) |

group developed an acute UTI (cystitis). During phase II, 4 patients in group A contracted an acute UTI (3, cystitis; 1, cystourethritis), as did 3 in group B (cystitis). During phase III (follow-up), 3 patients in group A and 4 in group B had an acute UTI of the lower urinary tract (cystitis). In each case, the drug resistance of the pathogen was identified and an antibiotic administered. The bacteria identified during the trial were *E coli, Pseudomonas aeruginosa, Proteus vulgaris, Proteus mirabilis, Enterobacter* species, and *Klebsiella* species.

The overall within-group comparison of the number of UTIs occurring during follow-up versus baseline is shown in Figure 3. In both ITT subpopulations (per-protocol or best-case), the number of UTIs was highly significantly different after treatment compared with baseline (Table IV). The highest significance was observed in group A whether the per-protocol or the best-case approach was used; $P = 0.0001$ (Wilcoxon's matched-pairs test) compared with baseline. Moreover, during phases I and II the differences in both groups compared with baseline were also highly significant (Table IV).

### *Compliance*

Drug compliance was rated as good by the investigator and the patients who attended all the control visits (per-protocol approach: group A, n = 20; group B, n = 13); no additional patients were excluded due to the use of a lower dosage or the interruption of therapy. In group A, attendance at visits was 95.4% (21 of 22), 90.9% (20 of 22), and 90.9% (20 of 22) during phases I to III, respectively. In group B, attendance decreased from 100%

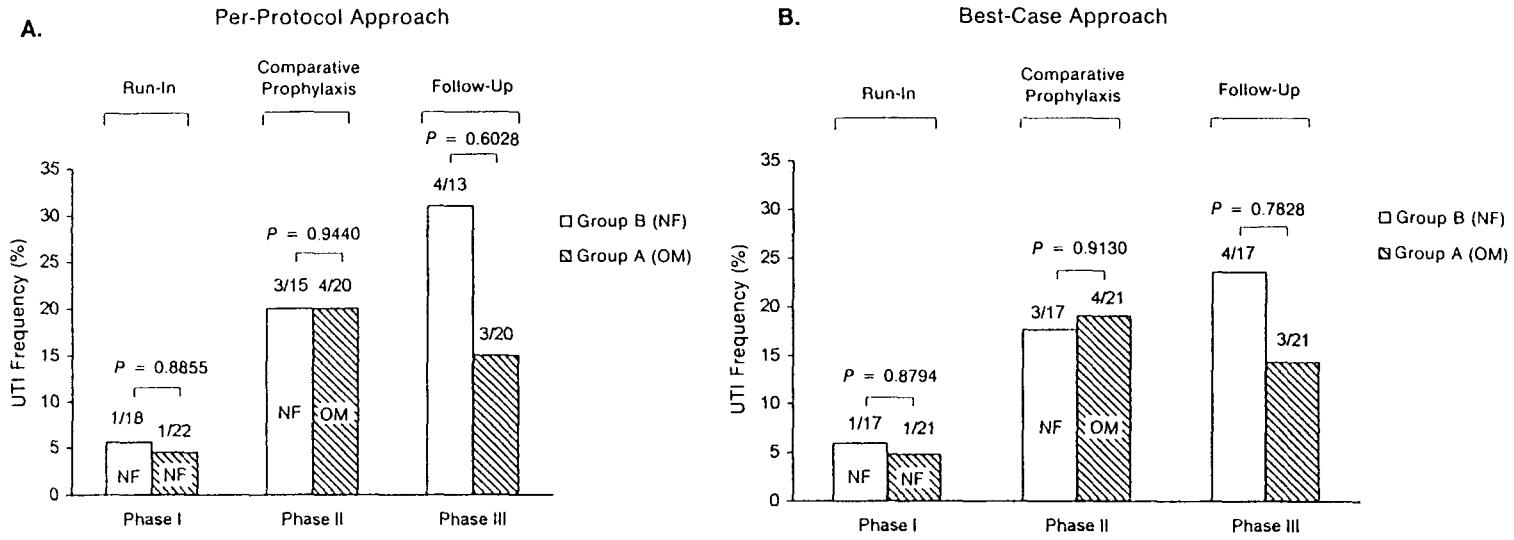


Figure 2. (*A*) Frequency and number of urinary tract infections (UTIs) diagnosed in patients in group A (OM-89) and B (nitrofurantoin) analyzed by a per-protocol approach (considering only valid cases without major and minor protocol violations [ie, pyelonephritis and missing data, respectively]). (*B*) Frequency and number of UTIs diagnosed in groups A and B analyzed by a best-case approach (excluding only major protocol violations [ie, pyelonephritis]). (*P* values between groups determined by the Mann-Whitney-Wilcoxon rank sum test.) NF = nitrofurantoin; OM = OM-89.

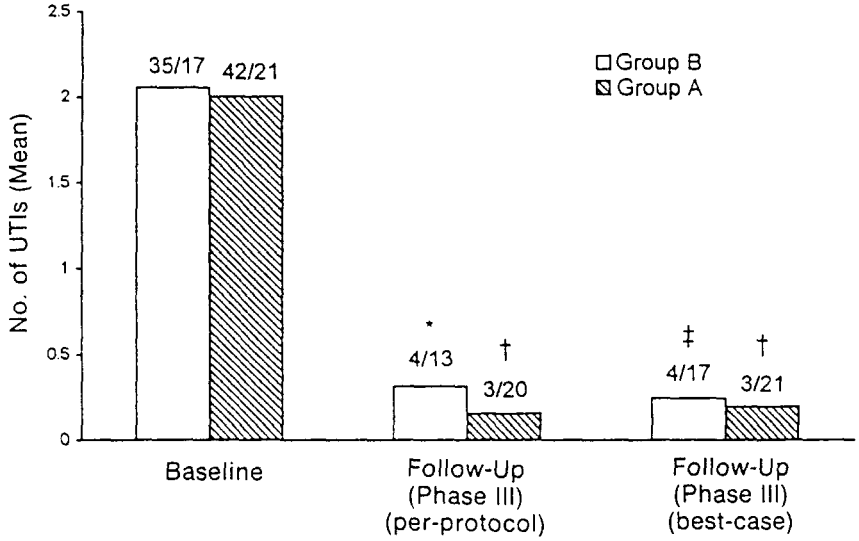


Figure 3. The mean number of urinary tract infections (UTIs) observed during the follow-up versus baseline in group A (OM-89) and group B (nitrofurantoin only), with a per-protocol or best-case approach. (Within-group comparison was analyzed using Wilcoxon's matched-pairs test comparing follow-up with baseline data within groups.) *$P$ = 0.0015; †$P$ = 0.0001; ‡$P$ = 0.0003, versus baseline.

(18 of 18) in phase I, to 83.3% (15 of 18) in phase II, and to 72.2% (13 of 18) in phase III. Patients given OM-89 (group A) were rated as having good attendance compliance (pills taken as prescribed); in contrast, patients given nitrofurantoin (group B) had poor attendance compliance (interrupted or discontinued medication).

### *Tolerability*

The tolerability of both long-term treatments was rated as good in the best-case ITT subpopulations (group A: 21 of 22 patients [95.4%]; group B: 17 of 18 patients [94.4%]). Except for patients with pyelonephritis, lack of attendance at control visits was because of the lack of symptoms and not because of side effects. Neither the investigator nor the patients reported any therapy-related adverse events.

## DISCUSSION AND CONCLUSIONS

The children admitted to this open-label study were representative of the usual population studied in the management of recurrent UTIs in childhood.[2,14–16] The results show that the oral OM-89 therapy (6 mg/d) was as efficient as nitrofurantoin (1 mg/kg/d) in decreasing the frequency of UTIs during treatment (phase II) and during follow-up (phase III) compared with prestudy data.

Table IV. Urinary tract infections (UTIs) during phases I, II, and III analyzed using the best-case and per-protocol approaches in group A (OM-89) and group B (nitrofurantoin). (Within-group analyses vs baseline [6-month prestudy data] performed with Wilcoxon's matched-pairs test.)

| | Phase I (vs Baseline) | Phase II (vs Baseline) | Phase III (vs Baseline) |
|---|---|---|---|
| Best-Case | | | |
| Group A | | | |
| No. of UTIs | 1 | 4 | 3 |
| No. of patients | 21 | 21 | 21 |
| *P* value | =0.0001 | =0.0001 | =0.0001 |
| Group B | | | |
| No. of UTIs | 1 | 3 | 4 |
| No. of patients | 17 | 17 | 17 |
| *P* value | =0.0003 | =0.0003 | =0.0003 |
| Per-Protocol | | | |
| Group A | | | |
| No. of UTIs | 1 | 4 | 3 |
| No. of patients | 22 | 20 | 20 |
| *P* value | =0.00005 | =0.0001 | =0.0001 |
| Group B | | | |
| No. of UTIs | 1 | 3 | 4 |
| No. of patients | 18 | 15 | 13 |
| *P* value | =0.0002 | =0.0007 | =0.0015 |

Throughout the study there were no statistically significant differences between the two treatment groups in the frequency of UTIs. During follow-up, a highly significant reduction was observed in both groups in the mean number of UTIs compared with baseline in the best-case ITT population (group A, $P = 0.0001$; group B, $P = 0.0003$). This highly significant decrease in infection rates occurred with both prophylactic regimens. The best-case ITT population analysis, as opposed to the per-protocol approach, was used to correct for the loss of patients in group B (the active control group), knowing that nonattendance at control visits was due to the lack of symptoms of UTI. Thus the best-case approach strengthens the power of the comparison between the patients who received OM-89 and the control patients who received only nitrofurantoin.

The enhanced immunologic defense obtained with OM-89 probably accounts for the long-term decrease in UTIs observed in phase III, as a result of the drug's consolidating effect on the patient's immune status. Another reason for this improvement is the instruction in proper perineal hygiene and ambulatory bladder training (drink adequate amounts of fluid, void frequently and completely, especially before bedtime) that was given to the patients with urinary incontinence.[7]

We found that the tolerability of both drugs was good. Nonattendance at control visits in patients in both treatment groups was not associated with the occurrence of side effects.

Other clinical studies have shown the efficacy of nitrofurantoin in the prevention of recurrences of UTIs.[16,18–20] Studies that used intermittent prophylaxis have shown better compliance and tolerability than studies that used continuous dosing.[21–24] Furthermore, antibiotics and various other chemotherapeutic agents have a spectrum of activity that does not cover numerous resistant organisms. Our observations confirmed the findings of other investigators[25,26] that *Proteus* species and *Pseudomonas* species are resistant to nitrofurantoin. Moreover, the incidence of adverse effects reported with nitrofurantoin is not negligible, whether of gastrointestinal, pulmonary, or neurologic origin[27–30]; although it is generally well tolerated, there has recently been some concern about the slight risk of pulmonary and hepatic fibrosis in children taking nitrofurantoin for prolonged periods.[31] Therefore, another advantage of nonspecific immune stimulation, as with OM-89, is the good tolerability with long-term use.

The results of this study are in accordance with other clinical studies carried out with adults using a double-masked, placebo-controlled design; OM-89 was shown to stimulate the immune defenses and to induce a significant drop in recurrent bacteriuria and dysuria, as well as antibiotic consumption, in patients with recurrent UTIs.[32–34] The activity of OM-89 is elicited by the stimulation of T-cells and of sIgA, the concentration of which was found to be significantly enhanced by OM-89 therapy in female children compared with controls.[35,36]

In conclusion, the stimulation of nonspecific immune defenses with OM-89 is a valuable alternative to and is at least as effective as the low-dose, long-term chemotherapeutic approach commonly used today for prophylaxis of UTIs in female children.

## *Acknowledgments*

The author thanks Laboratories OM S.A., Geneva, Switzerland, for providing the immunotherapeutic drug OM-89. Philippe Berthet, PhD, Biometrix S.A., Gland, Switzerland, for providing statistical analysis; and Claudio Amoruso, MSc, for his participation in the preparation and review of the manuscript.

*References:*

1. Tay JSH. Urinary tract infection in school children: Diagnosis and management. *Mother and Child.* 1977;3:8–12.

2. Jodal U, Winberg J. Management of children with unobstructed urinary tract infection. *Pediatr Nephrol.* 1987;1:647–656.

3. Chantler C, Carter JE, Bewick M, et al. 10 Years experience with regular haemodialysis and renal transplantation. *Arch Dis Child.* 1980;55:435–445.

4. McGowan JE Jr. Antibiotic resistance in hospital bacteria: Current patterns, modes for appearance or spread, and economic impact. *Rev Med Microbiol.* 1991;2:161–169.

5. Leski M. La cystite récidivante de la femme jeune. *Rev Med Suisse Romande.* 1983;103: 661–664.

6. Fliedner M, Mehls O, Rautenberg EW, Ritz E. Urinary sIgA in children with urinary tract infection. *J Pediatr.* 1986;109:416–421.

7. Riedasch G, Heck P, Rautenberg E, Ritz E. Does low urinary sIgA predispose to urinary tract infection? *Kidney Int.* 1983;23:759–763.

8. Hauser WE Jr, Remington JS. Effect of antimicrobial agents on the immune response. In: Ristuccia AM, Cunha BA, eds. *Antimicrobial Therapy.* New York: Raven Press; 1984:55–79.

9. Wybran J, Libin M, Schandene L. Enhancement of cytokine production and natural killer activity by an *Escherichia coli* extract. *Onkologie.* 1989;12(Suppl):22–25.

10. Van Pham T, Kreis B, Corradin-Betz S, et al. Metabolic and functional stimulation of lymphocytes and macrophages by an *Escherichia coli* extract (OM-89): In vitro studies. *J Biol Response Mod.* 1990;9:231–240.

11. Bosch A, Benedi VJ, Pares R, Joffre J. Enhancement of the humoral immune response and resistance to bacterial infections by the oral administration of a bacterial immunomodulator. *Immunopharmacol Immunotoxicol.* 1988;10(3):333–334.

12. Bottex C, Boyer G, Fontanges R. Efficacy of an immunomodulator in compensating antibiotic-induced immunosuppression. *Int J Immunopathol Pharmacol.* 1989;2:41–48.

13. Rubin RH, Shapiro EB, Androle VT, et al. Evaluation of new anti-infective drugs for the treatment of urinary tract infection. *Clin Infect Dis.* 1992;15(Suppl I):216–227.

14. McCracken GH. Diagnosis and management of acute urinary tract infections in infants and children. *Pediatr Infect Dis J.* 1987;6:107–112.

15. White RHR. Management of urinary tract infections. *Arch Dis Child.* 1987;62:421–427.

16. Working Group of the Research Unit of the Royal College of Physicians. Guidelines for the management of acute urinary tract infection in childhood. *J Royal College of Lond.* 1991;25:36–42.

17. Lettgen B. Harnwegsinfektionen im Kindesalter. *Klin Pädiatr.* 1993;205:325–331.

18. Kasanen A, Junnila SVT, Kaarsalo E, et al. Secondary prevention of recurrent urinary tract infection. Comparison of the effect of placebo, methenamine hippurate, nitrofurantoin and trimethoprim alone. *Scand J Infect Dis.* 1982;14:293–296.

19. Nunez U, Solis Z. Macrocrystalline nitrofurantoin versus norfloxacin as treatment and prophylaxis in uncomplicated recurrent urinary tract infection. *Curr Ther Res.* 1990;48: 234–245.

20. Raz R, Boger S. Long-term prophylaxis with norfloxacin versus nitrofurantoin in women with recurrent urinary tract infection. *Antimicrob Agents Chemother.* 1991;35:1241–1242.

21. Guibert J, Kitzis MD, Brumpt I, Acar JF. Activité antibactérienne de la péfloxacine dans l'urine durant sept jours après prise orale unique de 800 mg. *Pathol Biol (Paris).* 1989; 37:406–410.

22. Newcastle Covert Bacteriuria Research Group. Covert bacteriuria in schoolgirls in Newcastle on Tyne: A five year follow up. *Arch Dis Child.* 1981;56:585–592.

23. Fine JS, Jacobson MS. Single dose versus conventional therapy of urinary tract infections in female adolescents. *Pediatrics.* 1985;75:916–920.

24. Madrigal G, Odio CM, Mohs E, et al. Single dose antibiotic therapy is not as effective as conventional regimens for management of acute urinary tract infections in children. *Pediatr Infect Dis J.* 1989;7:316–320.

25. Verrier Jones K. Antimicrobial treatment for urinary tract infections. *Arch Dis Child.* 1990;65:327–330.

26. Winberg J, Berstrom T, Lidin-Janson G, Lincoln K. Treatment trials in urinary tract infection (UTI) with special reference to the effect of antimicrobials on the fecal and periurethral flora. *Clin Nephrol.* 1973;1:142–148.

27. Koch-Weser J, Sidel VW, Dexter M, et al. Adverse reactions to sulfisoxazole, sulfamethazole, and nitrofurantoin: Manifestations and specific reaction rates during 2118 courses of therapy. *Arch Intern Med.* 1971;128:399–404.

28. Holmberg L, Boman G, Böttinger LE, et al. Adverse reactions to nitrofurantoin: Analysis of 921 reports. *Am J Med.* 1980;69:733–738.

29. Penn RG, Griffin JP. Adverse reactions to nitrofurantoin in the United Kingdom, Sweden, and Holland. *BMJ.* 1982;284:1440–1442.

30. D'Arcy PF. Nitrofurantoin. *Drug Intell Clin Pharm.* 1985;19:540–547.

31. Coraggio MJ, Cross TP, Roscelli JD. Nitrofurantoin toxicity in children. *Pediatr Infect Dis J.* 1989;8:163–166.

32. Schulmann CC, Corbusier A, Michiels H, Taenzer HJ. Oral immunotherapy of recurrent urinary tract infections: A double-blind placebo-controlled multicenter study. *J Urol.* 1993;150:917–921.

33. Frey CH, Obolensky W, Wyss H. Treatment of recurrent urinary tract infections: Efficacy of an orally administered biological response modifier. *Urol Int.* 1986;41:444–446.

34. Hachen HJ. Oral immunotherapy in paraplegic patients with chronic urinary tract infections: A double-blind, placebo-controlled trial. *J Urol.* 1990;143:759–763.

35. Riedasch G, Käble T, Möhring K. Vaccination therapy of recurrent urinary tract infections of girls with Uro-Vaxom. *Z Antimikrobielle Antineoplastische Chemotherapie.* 1989;(Suppl 1):A257. Abstract.

36. Rosenthal M. Effect of a bacterial extract on cellular and humoral immune responses in humans. *J Immunopharmacol.* 1986;8:315–325.