Recurrent urinary tract infections in men. A role for aberrant bacterial forms

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الخلاصة

تم دراسة ٤٥ حالة مريض مصابين كحالة عرضية والذين يشكون من تكرار الاصابة بألتهابات المجاري البولية كحالة أنتكاسية بالاصابة البكتيرية. كل هولاء المرضى لم يتم أستخدام المخرج الانبوبي للتفريغ أو أية مادة أخرى تدخل الى المثانة او أستخدام تخريج الادرار وجمعه في حافظة خاصة لذلك الغرض . حيث تم فحص ١٠٠٠ نموذج للادرار لهولاء المرضى الذين كانوا يراجعون شعبة الجراحة في مستشفى حماد شهاب العسكري بين أذار ٢٠٠٠ الى نهاية تموز ٢٠٠٠ ولاجل مطابقة وتقييم ا لدراسة تم أجراء الفحص الموجب للمستضد المغلف للجرثومة الحاملة له من خلال وجودها في ترسب الادرار . من خلال هذه المرحلة تم أختيار مجموعة من المرضى لاجراء فحوصات شعاعية للجهاز البولي ولمتابعة التفريغ الادراري للجهاز البولي بعد المعالجة بمضادات الحياة والتي تم أختيارها وفق أسلوب الدواء المفضل بعد أجراء فحص الحساسية للدواء على تلك الجراثيم المسببة لتلك الالتهابات ومنها تبين أن تسعة مرضى قد شفوا شفاءا تاما أما البقية وهي (٣٦) حالة مرضية تم ملاحظة أن ٢٤ منهم قد أعاد الالتهاب لهم ثانية بعد تلك المعالجة وثمانية منهم تم أصابتهم ثانية ومنهم أربعة أعيدت الاصابة لوجود تلك الجراثيم ضمن كريات الدم البيضاء . لاتوجد حقيقة مرضية تنسب للجرثومة الشاذة والموجودة لدى المرضى لكونهم مرضى عرضيون مع أعادة أحتراق والتهاب الجهاز البولي..

ABSTRACT

We studied 45 infected a symptomatic men who had experienced recurrent urinary tract infections classified as bacterial relapse. These patients did not have ilial loop bladder, urethral catheters, suprupubic catheters or condom drainage. We had to process more than 1000 urines from patients attending the neurosurgery clinic at Hamad Shihab Hospital from March 2000 to July 2000 to identify the 45 study patients. A positive antibody coated bacteria influences test was detected on the urinary sediment of each of these patients.

This selected study group was subjected to excretory urography and a 2–weeks course of antibiotic in accordance with the results of in vitro susceptibility tests. Eight patients experienced a cure.

Recurrences developed in 32 patients (24 relapses, 8 reinfections). And in 4 patients a super infection emerged. No pathogenic role could be attributed to aberrant bacterial forms in this patient's population of symptomatic patients with recurrent invasive urinary tract infection.

INTRODUCTION :

Antibiotic treatment of men with urinary tract infections often fails to achieve the therapeutic goal, namely prolonged sterility of the urine[1,2,3]. A number of anatomical abnormalities, including infection stones, prostatic calculi, reflux nephropathy, papillary necrosis and obstructive uropathy, adequately explain many treatment failures[4]. We performed a prospective study of patients with recurrent invasive urinary tract infections to determine the impact provided by aberrant bacterial forms. Our study failed to implicate these organisms as a cause of recurrent, invasive urinary tract infections in these patients.

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MATERIALS AND METHODS :

Selection of patients: the study group consisted of 41 a symptomatic adult males previously identified by a screening procedure to detect bacteriurias, who attended the out patients clinic of the Hammad Shihab Hospital. To identify these men, we had to process man than 1000 urines. Three criteria had to be fulfilled for a patient be studied documentation had to exist in the patients medical record that he had experienced recurrent urinary tract infections, characterized as bacterial relapse during the preceding 3 years. These had to be significant bacteriuria with a pure culture of *pseudomonas aerogenosa* or a member of the enterobacteriaceae family that was susceptible in vitro, to the antibiotic prescribed. Significant bacteriuria was defined as the presence of $7x10^5$ colonies forming units/milliliters (CFU/ml) of urine of the identical organism in tow consecutive clean catch, midstream urine sample collected within 5 days before entering the study. Hastly the uninary sediment from the patient had to demonstrate a positive antibody – coated bacteria influences test.
The following patients were excluded from entrance into the investigation:
1 - Patients with ilial loop bladder.
2 - Urethral catheter.
3 - Suprupubic catheter.
4 - Condom drainage.
5 - Infection stones.
6 - Known vesico – ureteric reflux or a serum creatinine that exceeded 2 mg / dL.
No concomitant antimicrobial therapy was administered or invasive urological procedure performed during the study period. After uniformed consent was obtained, the patients relieved a 2 weeks course of oral antibiotic therapy in accordance with identification and susceptibility testing of the uninary isolate and the patient drug allergy history.
No patients refused to participate in the investigation the study was completed for a patient when drug intolerance, continuous bacteriuria, super infection rest reinfection or relapse occurred or successful microbiological response was achieved for a minimum of 6 weeks after termination the course of medication.
Each patients was subjected to excretory urography, cultures of the urine were performed 1,2,4,6 and 8 weeks after the onset of drug therapy. Urine samples were clean – catch, midstream voided samples all specimens were inoculated onto 5/tryptic soy sheep blood agar (Scott laboratory) and levine eosine methylene blue agar (Scott laboratory) plates by Jargensen tungsten allay, 4 mm calibrated wire loop calculated to deliver 0.01 / ml of urine, and then incubated aerobically at 37C̊ . Cultures were observed for growth for 24 hours and enterobacteriaceae and *Pseudomonas aeroginosa* were quantitated and then identify by many biochemical tests were employed. During the course of therapy and after the termination of drug administration any colony count that exceeded 10^4 CFU/ ml had to be confirmed by a second culture within four days.

Procedures to isolate aberrant bacterial forms :

Sediments from centrifuged urine collected 1,2,4,6 and 8 weeks after the onset of drug therapy were processed to attempt to isolate aberrant bacterial forms. To isolate cell wall defective bacteria a 10 ml. Portion of urine was centrifuged at 1000 x g for seven minutes and 0.1 ml. Of the sediment was inoculated on to each of two types of L-form agar and broth media with hypertonicity provided by the incorporation of NaCl and sucrose respectively.
Agar media consisted of trypticase Soya agar base (BBL – Microbiology Systems). To which was add 3% NaCl (w/v) for one medium and 10% sucrose (w / v) for the other media were supplemented with 10% (v/v) Todd - Hewitt broth (GIBCo Diagnostics). 5% (v/v) yeast extract (microbiological associates) and 10% (v/v) horse serum from defibrinated horse blood that had been inactivated by heating for 30 minutes at 56 C̊.

No antibiotic was added. The hypertonic media were prepared in biplates with NaCl – containing agar on one side and sucrose on the other. Both media were of the same formulation as the agar, with either Todd – Hewitt or trypticase Soya broth (BBL – microbiology systems). As base all media were incubated overnight at 35 C°. to establish sterility before use.
Duplicate biplates were inoculated and incubated at 35 C°. One aerobically and the other an aerobically. Broth cultures were incubated aerobically at 35 C°. under stationary conditions . All cultures were examined daily for four days and again on day 10 before discarding. Examination of the plates was made with magnifying hand lens and microscopically.
Subcultures of suspected colonies were made to L – form media and conventional media for definitive identification with the development of turbidity in broth, subcultures both aerobic and anaerobic were made to L – form media and examined for growth as above. All broth was evaluated at 10 days before discarding.

Immunological tests :

The antibody – coated bacteria immunofluoresence test was performed by the method developed by Thomas et al[5] .A specimen was arbitrary designated as positives when more than five uniformly fluorescent bacteria of at least grade (++) intensity were seen after viewing the sediment for a minimum five minutes .
Serological typing for determination of the somatic O- antigen were performed on *E. coli* , and Pyocenia production of *Psedomonas aerogenosa* was performed in the bacteriology laboratory .

Evaluation :

Reinfection occurs after medication has been continued and represent a recurrent bacterial infection produce by an organism different from that causing the original infection. Bacterial persistence also known as relapse defines that situation in which the pretreatment pathogen, having been temporary eliminated from the urine in response to therapy, survived within the urinary tract and subsequently initiated a recurrent infection. Colonial morphology, biochemical tests, anti microbial susceptibility testing and serotyping of the *E. coli* isolate and Pyocina producing by *Psedomonas aerogenosa* were the methods use to differentiate bacterial persistence from reinfection. Therapeutic success (cure) consisted of finding $< 10^4$ CFU/ml. Of urine for a minimum of six weeks after cessation of therapy. Super infection was defined as an infection characterized by consistent urine colony counts exceeding 10^4 CFU/ml. occurring during chemotherapy and caused by an organisms different from the pretreatment organism.

RESULTS :

Recurrence developed in thirty two patients (twenty four relapse, eight reinfections) and in four patients a super infection emerged. Each time bacterial relapse occurred, the organism remained susceptible to the antibiotic presented. Table 1 and 2 out line the excretory unography findings pretreatment urinary pathogen, antibiotic therapy treatment out come and results of processing urine to recover aberrant bacterial forms. We were unable to establish any causative role for aberrant bacterial forms in these patients with recurrent, invasive urinary tract infection.

Table 1 . Patient profile

Patient no.	I. V. P.	Pretreatment organism
5	Normal	*E. coli*
4	Normal	*Klebsiella aerogense*
4	Normal	*Proteus morganii*
4	Normal	*Citrobacter diversus*
8	Prostatic	*Pseudomonas aerogenosa*
8	Calcification Bilateral small kidneys	*Klebsiella aerogense*
8	Moderate postvoid Residual	*E. coli*
4	Normal	*Proteus mirabilis*

Table 2 . Therapeutic results

Patient no.	Therapy	Treatment results	Comments
5	Cephalexin 500 mg every 6 hours	Cure	Normal cystoscopy , normal ultrasound
4	Trimethprim–sulfamethaxazol 2 tablets every 12 hours	Cure	Normal Cystoscopy , normal ultrasound
4	Cephalexin 500 mg every 6 hours	Relapse	Extensive squamous metaplasia of bladder associated with acute and chronic inflammatory diabetes mellitus
4	Ampicillin 500 mg every 6 hours	Relapse	Urethral stricture
8	Carbenicillin sodium salts 1 mg every 6 hours	Relapse	Spondylolisthesis
8	Ampicillin 500 mg every 6 hours	Relapse	Urethral diverticulum
8	Ampicillin 500 mg every 6 hours	Reinfection	Recurrent epididymitis
4	Ampicillin 500 mg every 6 hours	Super infection	Urethral stricture

DISCUSSION :

This study underscores the observation that the conventional two weeks course of chemotherapy for men with recurrent invasive urinary tract infection has not been highly successful[(2)].

Invasion was manifest as a positive antibody – coated bacteria determination , a measure of deep , seated infection of the (uroepithelium) and a reliable indicator of tissue invasion in men with recurrent urinary tract infection[(6)].

Investigators have suggested that cell wall – defective bacteria contribute to chronic pyelonephritis and provide an explanation for the bacterial relapses that develop so frequently after chemotherapy has been discontinued .

After researchers assume a more coustious posture and express the opinion that the importance attached to the recovery of these aberrant bacterial forms has been exaggerated[7].

With the technique we employed, no cell wall – defective bacteria were isolated from the urine although patients received antibiotic capable of inducing aberrant bacterial forms. The use of media containing osmotic stabilizers did not detect L – form or other aberrant bacterial forms from multiple specimens obtained during the 6 weeks post treatment period. After drug therapy, no patients experienced a sequence in which the cell - wall defective form was isolated from the urine before the development of a recurrent urinary tract infection. Patients were not cautioned to restrict fluids before voiding, however and the possibility exists that the inability to ensure a high urinary osmolality precluded survival or recovery of aberrant bacterial forms.

Our study suggests that aberrant bacterial forms often fail to provide an explanation for the observation that urinary pathogens are able both to persist during therapy and to cause relapsing infections in the male urinary tract.

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