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Rheumatoid Arthritis is Caused by Asymptomatic Proteus Urinary Tract Infections

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1. Introduction

Urinary tract infections (UTI) are considered as one of the most common groups of infections in humans and affecting either the upper (kidneys--pyelonephritis) or the lower (bladder--cystitis) part of the urinary tract (Thomson and Armitage, 2010).

The gastrointestinal tract is a reservoir from which uropathogens emerge. Reflecting this, *Enterobacteriaceae* are the most important cause of UTI in all population groups, accounting for more than 95% of all UTIs. Among these microbes, *E. coli* is by far the most common invader, causing some 90% of UTIs in outpatients and approximately 50% in hospitalized patients. Whilst, the frequency of *P. mirabilis* causing outpatient and inpatients UTIs were 3.2% and 12.7% respectively, these value were reversed to 26.6% and 9.3% when all strains of *Proteus* species were examined (Talkoff-Robin et al, 2008). In a most recent multicentre study involving nine Spanish hospitals, 784 women with uncomplicated cystitis were evaluated for the frequencies of isolated uropathogens and their susceptibility to antibiotics. Among the 650 pathogens isolated, the first group of the most frequent bacterial agents was *Escherichia coli* (79.2%) followed by *Staphylococcus saprophyticus* (4.4%), *Proteus mirabilis* (4.3%), *Enterococcus faecalis* (3.3%), and *Klebsiella pneumoniae* (2.3%) (Palou et al, 2011).

In contrast to *E. coli* strains, it appears that all strains of *P. mirabilis*, regardless of isolate origin, are capable of infecting the urinary tract (Sosa et al, 2006). *Proteus* is particularly significant as a renal pathogen especially in causing upper UTI because of its propensity to promote struvite renal calculi (Ronald and Nicolle, 2007).

2. Asymptomatic bacteriuria and subclinical urinary infections

Bacteriuria might be either symptomatic or asymptomatic. An estimated 40% of women and 12% of men will experience at least one attack of symptomatic or overt UTI during their lifetime, and approximately a quarter of affected women will suffer recurrent UTIs within 6-12 months (Nielubowicz and Mobley, 2010).

Asymptomatic bacteriuria (ABU) is considered as one of the most common findings in women all over the world. It is defined as the presence of $\geq 10^5$ cfu/ml of the same bacterial species in two consecutive midstream urine samples (Schmiemann et al, 2010). Although in

the majority of patients with ABU the site of infection is in the lower urinary tract, some individuals with ABU, however, do have upper tract involvement (Ronald and Nicolle, 2007). In a cross-sectional longitudinal study, Kunin and associates have found that among 16,000 schoolgirls with ages ranging between 6 to 18 years the prevalence of UTI was 1.2%, and two-third of 5% girls who had one or more episodes of bacteriuria were asymptomatic (Kunin, 1970). It also appears that the prevalence of asymptomatic bacteriuria increases with age and this has been reported by Gaymans et al (1976), where in a study of 1,758 Dutch women, the prevalence of bacteriuria was found to be increased from 2.7% of women aged 15 to 24 years to 9.3% of women aged 65 years or older.

Although it is usually true to say that bacteriuria is a valid indicator of either bacterial localization or infection of the urinary tract, studies in animals (Mulvey et al, 1998) and humans (Elliott et al, 1985) have indicated that bacteria may reside in the urothelium in the absence of bacteriuria. The majority of patients with kidney or upper tract infection show the clinical signs and symptoms of pyelonephritis, but in others this might not be the case. In a study by Stamey et al (1965), using ureteral catheterization it was shown that 50 percent of women with asymptomatic bacteriuria had infection in their upper tracts, and that a small but significant proportion of women with preliminary associated cystitis also had upper UTI. It is possible that bacteria within the kidney or upper urinary tract may remain latent in a nidus of infection for any length of time (Cattell, 2005). For example *Proteus* spp. can form urinary calculi and remain dormant inside these infected stones undetected and resistant to the effects of antibiotics used. It should also be stressed that *P. mirabilis* is probably the second most common microbe among the family of *Enterobacteriaceae* after *E. coli* in causing UTI, especially of the upper tract in middle-aged and elderly women (Senior, 1979).

3. Rheumatoid arthritis and urinary tract infections

Rheumatoid arthritis (RA) is a potentially disabling chronic systemic polyarthropathy with a world-wide distribution and an increased likelihood to have a considerable amount of negative impacts on the economical status of the patient and society (Zhang and Anis 2011). The cause of this disease is generally agreed to be due to a combined action of genetic and environmental (mainly microbial) factors (Firestein, 2009).

Among the urologists and rheumatologists, the evidence of the link between UTIs and RA is not apparently recognized because of the consistent lack of data supporting this association and more probably because of the possibility for an existing hidden infection expressed in the form of asymptomatic bacteriuria in patients with RA.

In a preliminary study carried out by a group from Tel Aviv, it has been found that 35 percent of patients with RA and secondary Sjogren's syndrome had recurrent attacks of UTIs (Tishler et al, 1992). Furthermore, another group from Edinburgh, using a necroscopic examination of kidneys from dead patients with RA, found that approximately 17.6 percent of males and 22.7 percent of female patients showed signs of chronic pyelonephritis (Lawson and Maclean, 1966). A similar result was found in a previous study carried out by a group from Copenhagen, where a considerably high degree of associated non-obstructive pyelonephritis and renal papillary necrosis was detected among the renal autopsy materials from patients with RA (Clausen and Pedersen, 1961). However, this kind of association between RA and UTIs was not always observed (Vandenbroucke et al, 1987). This discrepancy in the results with an apparent lack of the epidemiological link between urinary

infections and RA could be due to the occurrence of sub-clinical or occult infections, which are merely characterized by bacteriuria.

4. *Proteus* in the urine of patients with RA

RA is most probably caused or initiated by an upper urinary tract infection with *Proteus* bacteria. Regarding this particular subject, more than 100 articles have been published by our and various other collaborative as well as independent groups throughout the world (Ebringer et al, 2010).

The first evidence of a link between *Proteus* microbe and RA was reported nearly three decades ago where in a study by Chandler and co-workers, it was shown that among a panel of 30 microbial agents tested, the mean geometric titres of antibodies were raised only against *Proteus* OXK and herpes virus hominis microbes in 22 newly diagnosed RA patients when compared to 22 control subjects (Chandler et al, 1971). Meanwhile, this disease-microbe association was established fourteen years later in a study by our group, where a significant elevation of *Proteus* antibodies ($p < 0.001$) was shown in 30 patients with RA compared to 41 healthy controls (Ebringer et al, 1985). To search for the source of this microbe in urinary tract of RA patients various studies were carried out by our and other independent groups:

1. In a controlled study of 89 patients with RA from London, *P. mirabilis* was isolated from the urine of 63% of female and 50% of male patients and these results were found to be significant in comparison to female (32%) ($p < 0.001$) or male (11%) ($p < 0.001$) healthy subjects. However, the frequency of the isolation of *Proteus* from urine of men and women patients without RA (osteoarthritis, fibromyalgia, psoriasis, gout, and systemic lupus erythematosus) was 7% and 35% respectively, which were similar to those obtained from healthy men (11%) and women (32%) individuals (Figure 1). Furthermore, a positive correlation was found between high anti-*Proteus* antibody levels in sera of RA patients and the number of colony-forming units obtained from urine specimens of these patients (Wilson et al, 1997).
2. In another study carried out by a group of scientists from Dundee in the UK, a significantly increased isolation rate of *Proteus* microbes from the urine of 76 patients (33%) were detected when compared to those of 48 gender-matched healthy individuals (4%) (Senior et al 1999) and this isolation rate was found to be occurring twice more frequently as *E. coli*. In the same study significant elevations ($p < 0.001$) of antibodies against *P. mirabilis* were detected in the urine and serum samples of patients with RA when compared to the corresponding healthy subjects.

Another group, however, was unable to find a significant increase in the isolation of *Proteus* microbes from the urine or faeces of RA patients (McDonagh et al, 1994).

5. *Proteus* virulence factors and cross-reactive antigens

The main virulence factors which have been involved in the uropathogenetic mechanisms and utilized by the major group of uropathogens, namely *E. coli* and *P. mirabilis* include motility, adherence, biofilm formations, β -lactamase productions, toxin productions, hydrolytic enzyme productions, metal acquisitions and evasion of the host immune defenses (Dobrindt, 2010).

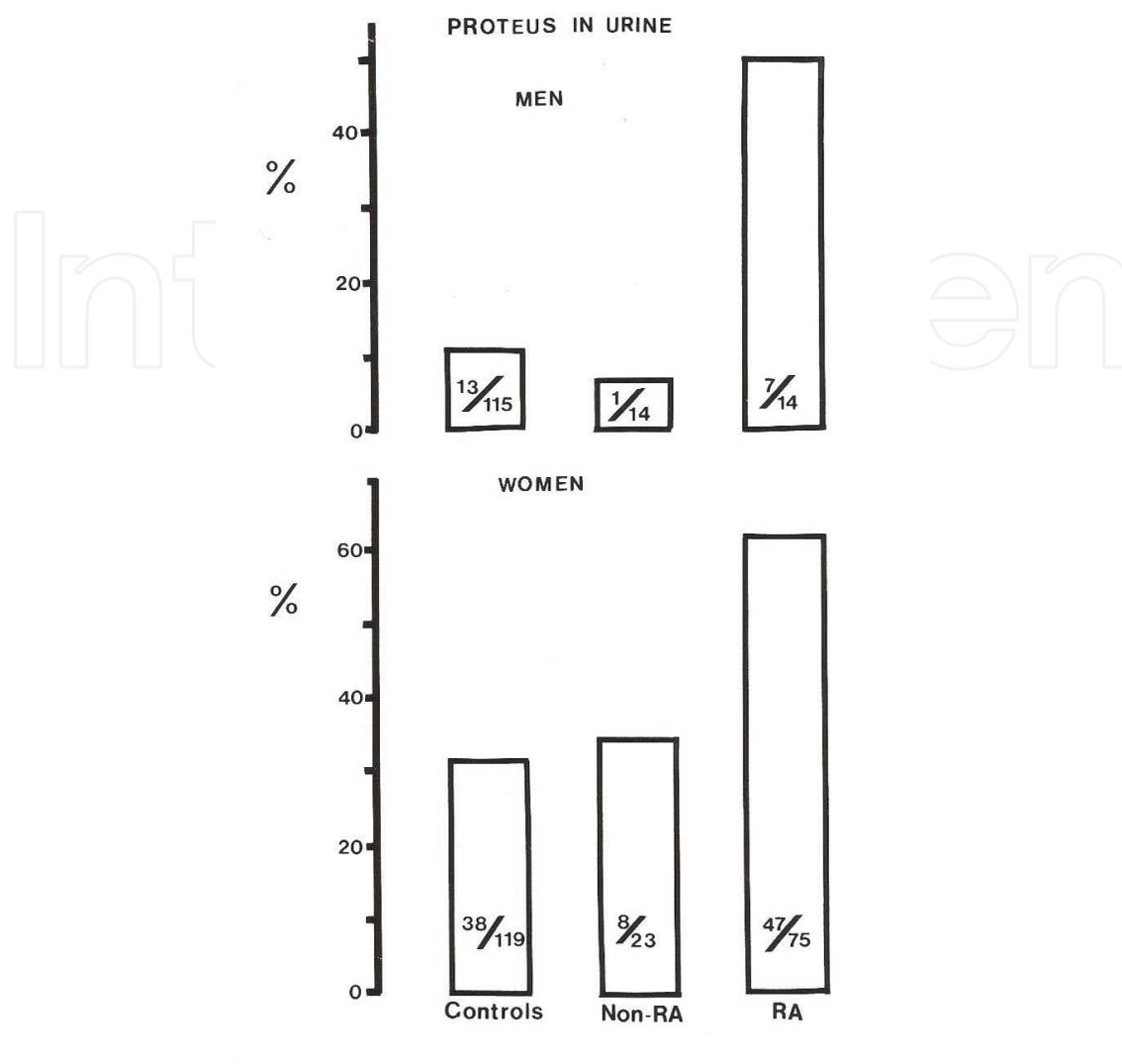


Fig. 1. Percentage isolation of *Proteus* bacteria from the urine of rheumatoid arthritis (RA) and non-RA patients and healthy controls. (Urine cultures were measured down to the level of 1 cfu/ml of urine, to determine presence or absence of bacterial signal).

In contrast to *E. coli*, *P. mirabilis* is the main producer of the urease enzyme (Rozaliski et al, 1997), which hydrolyzes urea into ammonia and carbonate. One of the hallmarks of UTI caused by *P. mirabilis* is the production of urinary stones through action of urease. These stones which are a composite of magnesium ammonium phosphate crystals (struvite), might act as infective reservoirs of *Proteus* microbes, and basically protected from host defenses and antibiotic treatment (Li et al, 2002).

Proteus microbes possess various different antigens. Two of these were found to resemble self tissue antigens. The *Proteus* haemolysin protein possesses six amino acid molecules "ESRRAL" which resembles a similar amino acid motif "EQRRAA" present in the HLA-DR1/4 genetic molecules (Wilson et al, 1995) frequently found in association with RA (Stastny, 1976). Whilst another group of antigens comprising five amino acid molecules "IRRET" which is present in *Proteus* urease resembles the "LRREI" motif present in type XI collagens (Wilson et al, 1995), which is found in hyaline cartilage of the joint tissues.

6. *Proteus* antibodies and their role in the pathogenetic mechanism of RA

Elevated levels of antibodies to *P. mirabilis* have been detected in patients with RA among many populations from 14 different countries including UK, USA, France, and Netherlands (Ebringer et al, 2010). These results have been detected by using various immunological methods carried out by collaborative (Table 1) and other independent (Tables 2) groups. The specificity of *Proteus* antibodies in patients with RA was shown in many studies. Deighton et al, found that antibodies to *P. mirabilis* but not to four different viruses (Deighton¹ et al, 1992) were elevated significantly in RA patients. Moreover, in a review analysis it was shown that in patients with RA there were significant elevations of antibodies to *Proteus* but not against more than 20 other enterobacterial or uropathogenic microbes, including *E. coli* (Rashid et al, 2007).

As the result of molecular mimicry or similarity between *Proteus* and self antigens, patients infected with *Proteus* microbes will produce not only antibodies against this microbe but also against the self tissue molecules carrying the cross-reactive antigens. These antibodies will bind to and be cytopathic to the joint tissues which carry *Proteus* cross-reactive antigens (Wilson et al, 2003) and this immune reaction will lead to the release of more self tissue antigens with a consequent production of further autoantibodies, propagation of the pathological process and the development of classical RA, in the same way that *Streptococcus* causes rheumatic fever and valvular lesions in the heart (Guilherme et al, 2011).

7. A proposal for a new treatment in RA—eradication of *Proteus* microbes

Currently the pharmacologic treatment of RA mainly involves the use of disease modifying anti-rheumatic drugs and biological agents (Haraoui and Pope, 2011). In concurrent use with these medical treatments other therapeutic measures can be employed in order to eradicate *Proteus* bacteria from the urinary tract which could help to prevent further tissue and joint damages in patients with RA. These measures could involve the use of cranberry juice products, antibiotics or even vaccination.

Cranberry products have been used widely for several decades for the prevention and treatment of UTIs. A meta-analysis has established that recurrence rates of UTIs over 1 year are reduced approximately by 35% in young to middle-aged women (Guay, 2009). Other studies, however, either supported (Ferrara et al, 2009) or disputed (Barbosa-Cesnik et al, 2011) the effect of cranberry preparations in the prevention of UTIs.

Although the use of anti-microbial agents has not been recognized in the management of RA, some antibiotics have already been tried with encouraging results. Among these are sulphasalazine, metronidazole, rifampicin and minocycline (Ebringer et al, 2003). Some problems, however, exist in regard to the use of antibiotics against *Proteus* microbes. Firstly, *Proteus* infection affects mainly the kidneys and upper urinary tract (Fairley, et al, 1971) where the use of ordinary sterilizing substances and antibiotics can be less effective. Secondly, *P. mirabilis* possesses various virulence factors which enhance its urinary epithelial invasiveness rendering this microbe resistant to antibiotics (Mathoera et al, 2002). Thirdly, when an infected struvite stone is present in the kidney, none of the antibiotic agents seems to be effective unless the stone is removed by surgery or shock-wave therapy.

In order to test the effects of antibiotics in patients with RA through prospective longitudinal studies, the search for an effective anti-*Proteus* chemotherapeutic agent is mandatory. In a most recent study from Japan it was shown that all of the *P. mirabilis* strains including extended system β -lactamase (ESBL)-producing strains were susceptible to penicillin derivatives combined with β -lactamase inhibitors (Ishikawa et al, 2011). In another

study, it was shown that among the three carbapenems tested, meropenem was the most potent antibiotic being effective against the majority of the *Proteus* species isolates (Lee et al, 2011). If patients with RA respond to anti-microbial measures, prophylaxis of susceptible individuals could be instigated by the mean of immunization with attenuated antigens from causative microbe or other cross-reactive microbes among the *Enterobacteriaceae* group (Scavone et al, 2011).

It is logical to start treating patients with RA from early stages of the disease in order to prevent further irreversible joint damages from occurring. If such early therapy is undertaken the possibility arises that RA may be eradicated in the same way that rheumatic fever has been eliminated in the Western World by the means of early treatment of *Streptococcal* tonsillitis with penicillin and other related antibiotics.

8. General discussion

It generally appears that there is an apparent relationship between *Proteus* asymptomatic UTIs and RA. The main hallmark of this association is based on showing the linkage between RA and *Proteus* but not other microbes in the majority of studies carried out by various groups throughout the world. The combination of isolation of *Proteus* microbes in the urine and elevation of antibodies in sera of RA patients as well as the evidence for the cytopathic effects of these antibodies against the joint tissue cross-reactive antigens, forms the major evidence for the role of this microbe in the development of RA. Elimination of *Proteus* microbes by using cranberry juice, antibiotics could have a remarkable effect in the management of RA patients alongside currently used anti-rheumatic drugs. It would appear that the management of RA may be relevant to urologists as well as to rheumatologists.

YEAR	RA	HC	METHOD	P VALUE	REFERENCE
1985	30	41	AM	P<0.001	Ebringer et al
1988	32	18	ELISA	P<0.05	Khalafpour et al
1995	50	49	ELISA	P<0.001	Fielder et al
1995	40	30	ELISA	P<0.001	Wilson et al
1995	34	33	ELISA+IIF	P<0.001	Subair et al
1996	66	60	ELISA	P<0.001	Tiwana et al
1997	50	50	ELISA	P<0.001	Tani et al
1997	89	234	ELISA	P<0.001	Wilson et al
1997	60	60	ELISA	P<0.001	Tiwana et al
1998	25	34	IIF	P<0.001	Blankenberg-Sprenkels et al
1999	114	69	IIF	P<0.001	Rashid et al
2003	51	38	ELISA	P<0.001	Wilson et al
2004	159	53	IIF	P<0.001	Rashid et al
2006	50	38	ELISA	P<0.0001	Rashid et al
2007	70	20	ELISA	P<0.001	Rashid et al

RA = rheumatoid arthritis; HC = healthy controls; AM = agglutination method ; ELISA = enzyme-linked immunosorbent assay; IIF = indirect immunofluorescence.

Table 1. Studies carried out by various collaborative groups showing increased anti-*Proteus* antibodies in patients with RA compared to HC individuals (number of subjects indicated in each study).

YEAR	RA	CONTROLS*	METHOD	P VALUE	REFERENCE
1988	29	30	ELISA	P<0.01	Rogers et al
1991	9	10+10 (AS+HC)	ELISA	p<0.01; NS	Murphy et al
1992	142	121	IIF	P<0.0001	Deighton ² et al
1994	87	29 (non-RA)	IIF	P<0.003	McDonagh et al
1995	27	27 (non-RA)	ELISA; IB	P<0.0001	Senior et al
1996	40	40	ELISA	P<0.001	Dybwad et al
1997	70	82	AM	P<0.001	Wanchu et al
1999	39	51	ELISA	p<0.001	Chou et al
2003	50	25	AM	P<0.001	Gautam et al
2005	59	63	IB	P<0.01	Weisbart et al
2005	246	43+90 (SpA+UA)	ELISA	P<0.0003; p<0.015	Newkirk et al

*Controls are always healthy individuals unless otherwise stated; RA = rheumatoid arthritis; AS = ankylosing spondylitis; HC = healthy control; SpA = spondyloarthropathy; UA = undifferentiated arthritis; ELISA = enzyme-linked immunosorbent assay; IIF = indirect immunofluorescence; AM = agglutination method; IB = immunoblot; NS = not significant.

Table 2. Studies carried out by independent groups showing increased anti-*Proteus* antibodies in patients with RA compared to controls.

9. Acknowledgements

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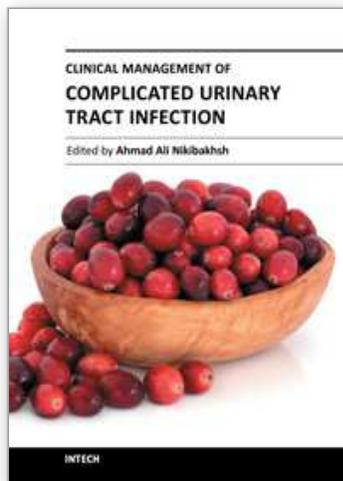
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Complicated urinary tract infections (cUTIs) are a major cause of hospital admissions and are associated with significant morbidity and health care costs. Knowledge of baseline risk of urinary tract infection can help clinicians make informed diagnostic and therapeutic decisions. Prevalence rates of UTI vary by age, gender, race, and other predisposing risk factors. In this regard, this book provides comprehensive information on etiology, epidemiology, immunology, pathology, pathogenic mechanisms, symptomatology, investigation and management of urinary tract infection. Chapters cover common problems in urinary tract infection and put emphasis on the importance of making a correct clinical decision and choosing the appropriate therapeutic approach. Topics are organized to address all of the major complicated conditions frequently seen in urinary tract infection. The authors have paid particular attention to urological problems like the outcome of patients with vesicoureteric reflux, the factors affecting renal scarring, obstructive uropathy, voiding dysfunction and catheter associated problems. This book will be indispensable for all professionals involved in the medical care of patients with urinary tract infection.

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