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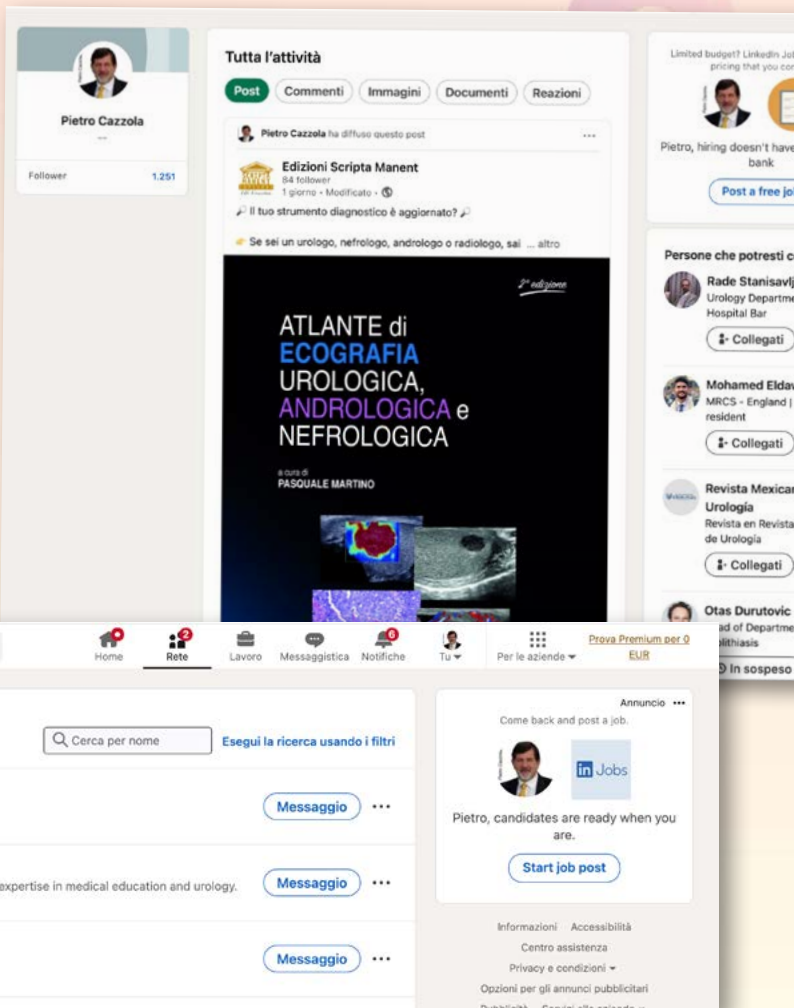


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Treatment of asymptomatic bacteriuria from *Proteus mirabilis* may reduce the potential risk of rheumatoid arthritis development and progression

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SUMMARY

Rheumatoid arthritis (RA) is a chronic systemic and arthritic autoimmune disease that affects millions of people worldwide. It is characterized by inflammation of the joints which can lead to the destruction of the periarticular tissue, causing thus chronic pain, joint deformities and consequently disability and deterioration of quality of life. During the last decades, scientific data has suggested that *Proteus* spp. have a key role in the aetiopathogenesis of RA. Current Guidelines on asymptomatic bacteriuria suggest to treat only patients that will benefit from treatment such as pregnant woman patients

undergoing urologic procedures in which mucosal bleeding is expected and patients who are in the first month following renal transplantation. Given the involvement of *Proteus* on RA pathophysiology, treatment of asymptomatic bacteriuria from *P. mirabilis* may reduce the potential risk of RA development and progression. Here, we performed a review of the available literature regarding the association between RA and UTI caused by *Proteus* spp., and we discuss the abovementioned issue.

Key words: asymptomatic bacteriuria, *Proteus mirabilis*, rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of unknown etiology. Chronic inflammation of the synovial tissues is the most prominent symptom however, manifestations of systemic inflammation are also common (1). Since remission and recurrency are usual in RA, patients report gradual impairment of all aspects of QOL. As a consequence, RA is associated with increased mortality and reduced life expectancy (2). Extensive literature based on the results of various genetic, microbiological, molecular, and immunological studies shows that a strong link exists between

RA and the presence of *Proteus mirabilis* microbes in the urinary tract (3). In a such a case, treatment of asymptomatic bacteriuria from *P. mirabilis* may reduce the potential risk of RA development and progression.

Asymptomatic bacteriuria is defined as the presence of bacteria in the properly collected urine of a patient who has no signs or symptoms of a urinary tract infection. It is very common in clinical practice and its incidence increases with age. In women and men aged 65 to 80 years, the incidence is 15 per cent or more, and after the age of 80 it is as high as 40 to 50 per cent. Accumulated evidence provides few indications to treat asymptomatic bacteriuria. In fact, most patients with asymptomatic bacteriuria will

never develop symptomatic urinary tract infections and will have no adverse consequences from asymptomatic bacteriuria, while some investigators showed that inappropriate treatment contributes to the development of antimicrobial resistance (4). For this reason, current guidelines recommend screening and appropriate treatment for asymptomatic bacteriuria only in pregnant women, in individuals undergoing endourological procedures associated with mucosal trauma and patients who are in the first month following renal transplantation (5). No mention on *Proteus mirabilis* and Rheumatoid arthritis (RA) exists in the current guideline on asymptomatic bacteriuria so far. In this paper we analyse the role of *Proteus mirabilis* bacteria in the etiopathogenesis of RA and discuss the potential benefit of treating asymptomatic bacteriuria from *P. mirabilis*.

MATERIAL AND METHODS

A database and a manual search were conducted in the MEDLINE database of the National Library of Medicine, PubMed, EMBASE, the Cochrane Library and other libraries using the key words “Asymptomatic bacteriuria”, “Rheumatoid arthritis”, “*Proteus mirabilis*”, in various combinations with the terms “etiopathogenesis”, “progression” “treatment”, “remission”, “guidelines”, “infection”. Two independent reviewers performed data extraction by using identical extraction tables. We included all clinical studies with available information. We considered full-text written papers. We also included reviews and case reports. Bibliographic information in the selected publications was checked for relevant records not included in the initial search.

RESULTS

The exact mechanism of RA development has not been fully investigated. However, a combination of synovial tissue destruction processes (involving lymphocytes, macrophages, and fibroblasts) with increased angiogenesis rates and proliferation of the synovium lining layer characterizes the initiation of RA development. Progression of RA includes immune-mediated destruction of the bone and cartilage resulting in permanent impairment of the joint's function (6). The complex cascade of inflammatory interactions characterizing RA is mediated by cell adhesion molecules (CAMs) such as P-selectin, E-selectin, and intercellular adhesion molecule-1 (ICAM-1). These glycoproteins mediate cell-cell and cell-extracellular matrix adhesion which appears to play an important role in the initiation and the perpetuation of synovial tissue inflammation (7,8). Specifically, in response to inflammatory conditions, stimulated by tumor necrosis factor α (TNF α), interleukin-1 (IL-1) and lipopolysaccharide (LPS), P-selectin -normally stored in the Weibel-Palade bodies of endothelial cells and in the alpha granules of platelets- is released to the cell surface where it produces CD40 ligand (sCD40L)

that increase vascular permeability (9). The abovementioned expression of P-selectin induces the over-expression of E-selectin on endothelial cells of nearby blood vessels which recruit leukocytes. Leukocytes expressing the correct ligand bind with low affinity to E-selectin and roll thorough the vessels to the site of injury where they bind tightly to the endothelial surface and begin making their way into the tissue (10). Contemporarily, inflammatory cytokines induced up-regulation of ICAM-1 expression on vascular endothelial cells, contribute further to the adhesion of leucocytes to the local endothelium and subsequently in their migration to inflamed tissues (11).

Three studies compared samples of healthy individuals with those of RA patients and found that RA patients have significantly elevated levels of serum antibodies against various antigens from *P. mirabilis* (Table 1) (12-14). Serological analysis of the samples of a cohort of 246 patients with inflammatory arthritis revealed a strong correlation between IgM anti-*Proteus* antibody levels and rheumatoid factor RF (15). Importantly, in the 10 serum samples belonging to the patients with the highest levels of RF who also had high anti-*Proteus* IgM antibody titres, it was not observed a significant drop in anti-*Proteus* IgM titre after removal of RF (15).

Older studies have demonstrated high levels of soluble adhesion molecules (ICAM-1, VCAM-1, P-selectin and E-selectin) and vascular endothelial growth factor (VEGF) in the serum of RA patients (16,17). Newer studies correlated the levels of the above soluble adhesion molecules with the levels of antibodies to cross-reactive and non-cross-reactive antigens from *Proteus* microbes (18,19). A strong correlation between serum and synovial fluid concentration of soluble selectin with RA activity exists (20) and levels of soluble-selectin and sCD40L in the serum of RA patients with *Proteus mirabilis* correlates with RA severity (21).

DISCUSSION

RA is a significant health concern worldwide. The global prevalence of RA has been on the rise. From 1990 to 2019, the age-standardized prevalence rate increased from 207.46 per 100,000 people to 224.25, with an estimated annual percent change (EAPC) of 0.37%1. Regarding incidence, the age-standardized incidence rate (ASR) increased from 12.21 per 100,000 people in 1990 to 13 in 2019, with an EAPC of 0.3%1. Disability-Adjusted Life Years (DALYs) represent the combined impact of premature death and disability due to a disease. For RA, DALYs increased significantly from 3.3 million in 1990 to 4.8 million in 2010. This increase is attributed to population growth and aging (22).

The global burden of RA will continue to escalate in the coming years, emphasizing the need for early diagnosis and effective treatment strategies to alleviate this burden (23). Relevantly, for the past four decades, UTI caused by *Proteus* spp. has been suggested as a key player in the

aetiopathogenesis of RA, and this correlation has been documented in populations of different countries from Europe, Asia, and North America being an association based in either serum or urine samples, all with significant results. It should be mentioned that serum antibodies against various antigens from *P. mirabilis* can be detected in RA patients early with the onset of the disease (12,15). In confirmation to the above, studies in mouse model of RA showed that autoantibodies, after a few minutes of intravenous injection migrate specifically in joints even in the absence of pre-existing joint inflammation (24). Notably, many of RA patients have no evident infection of the urinary tract and for this reason some investigators suggested that sub-clinical *Proteus* urinary tract infections are the main triggering factors of RA development (6,25). The most likely mechanism in the *Proteus* induced RA is “molecular mimicry” where *Proteus* antigens were found to share homologous sequences, which cross-react with certain self-antigens present in synovial tissues that could lead to the production of antibodies targeting both bacteria and self-tissues (26). Given that *P. mirabilis* causes between 1% and 10% of all urinary tract infections, and

asymptomatic bacteriuria with *P. mirabilis* is particularly common in the elderly and patients with type 2 diabetes (27), treatment of asymptomatic bacteriuria from *Proteus mirabilis* may reduce the potential risk of rheumatoid arthritis development and progression in a considerable number of patients. To our knowledge, previous studies have showed that anti-*Proteus* antibiotics in combination with anti-rheumatic drugs in RA patients had a better response in the disease activity especially during the early stages of the disease (28).

CONCLUSION

The association between RA and UTI caused by *Proteus* spp., has been investigated in depth in different countries worldwide. Currently, there is no specific guideline for patients with asymptomatic bacteriuria involving *Proteus*, however the above evidence suggests that *Proteus* anti-bacterial treatment protects both RA patients as well patients without RA from RA recurrency and development respectively.

Autor	Study group	Sample	Comparison of RA pts findings to those of the controls
Senior B., et al.	76 RA patients 48 healthy individuals	urine serum	Extremely or very significantly higher IgM, IgG, and IgA levels to <i>P. mirabilis</i> in the sera Extremely significantly the IgM, IgG, and IgA levels to <i>P. mirabilis</i> in the urine
Christopoulos G., et al.	63 RA patients 38 healthy individuals	serum	Accurately elevated levels of IgM, IgG, and IgA antibodies against hemolysin <i>Proteus</i> peptide (anti-HpmB), against UreC <i>Proteus</i> peptide (anti-UreC), and against UreF <i>Proteus</i> peptide (anti-UreF).
Rashid T, et al. (2004)	132 RA patients 50 healthy individuals	serum	Elevated levels of IgA, IgG, IgM anti- <i>Proteus</i> antibodies. Elevated levels among the IgG class of antibodies to EQRRAA and ESRRAL peptides.
Deighton C., et al. (29)	146 RA patients	serum	Only <i>Proteus</i> antibodies antibodies are significantly increasing in active RA.
Newkirk M., et al.	246 patients with inflammatory arthritis	serum	Moderate correlations between anti- <i>Proteus</i> IgA, IgM, and IgG antibody levels with total serum IgA, IgM, and IgG levels Strong correlations between the titre of IgM antibodies to <i>P. mirabilis</i> and the RF titre
Rashid T, et al. (2007)	70 RA patients 20 healthy controls	serum	Significantly elevated levels of total and class-specific IgG antibodies against the 3 <i>Proteus</i> peptides More than 90% of active RA patients showed positive values for the <i>Proteus</i> anti-peptide indices

Table 1. Most important research investigating the association between RA and *Proteus* spp.

Authors contributions

All authors whose names appear on the submission

1. Made substantial contributions to the conception of the paper
2. Drafted the work or revised it critically for important intellectual content
3. Approved the version to be published.

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How to prevent prostate cancer by eating

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Advising patients how to prevent prostate cancer with proper nutrition I believe is a duty for every urologist. This article is aimed at younger colleagues to give accurate guidance.

Prostate cancer is one of the leading causes of illness and mortality among men, with approximately 1.6 million new diagnoses and 366,000 deaths annually. Understanding the risk factors and the role of diet in prevention is crucial.

RISK FACTORS

- **Age:** Prostate cancer is rare in men under 40, but its incidence rises sharply after age 55.
- **Ethnicity:** In the U.S., African American men have three times higher incidence rates and 2.4 times higher mortality rates than other populations.
- **Family History:** Men with a father or brother diagnosed with prostate cancer have a two to three times greater risk.
- **Height:** Greater height may increase the risk, possibly linked to early exposure to growth hormones.
- **Obesity:** A higher BMI is associated with a 20% increased risk of prostate cancer mortality.
- **Smoking:** Current smokers have a 60% higher risk of dying from prostate cancer.
- **Physical activity:** Regular vigorous exercise can reduce



the risk of advanced prostate cancer by 77% and improve survival rates.

- **Cholesterol and Statins:** High cholesterol levels may raise the risk, while statins are linked to a 34% reduction in mortality.

NUTRIENTS AND PROSTATE CANCER PREVENTION

- **Tomatoes:** Rich in lycopene, a powerful antioxidant, cooked tomatoes offer higher bioavailability of lycopene, potentially lowering prostate cancer risk.
- **Cruciferous vegetables:** Broccoli, Brussels sprouts, and cauliflower are associated with a reduced risk.
- **Carrots:** Studies indicate a significant reduction in prostate cancer risk with carrot consumption.
- **Green Tea:** Catechins in green tea may help reduce prostate cancer risk.
- **Coffee:** Moderate coffee consumption (three cups per day) is linked to a lower risk of fatal prostate cancer.
- **Fish:** Omega-3 fatty acids in fish are associated with a reduced risk of prostate cancer mortality.
- **Dairy:** Excessive dairy intake, especially cheese, has been linked to an increased risk of fatal prostate cancer.

CONCLUSION

A Western diet, high in processed meats, fats, and refined sugars, increases the risk of advanced prostate cancer. In contrast, the **Mediterranean diet**, rich in fruits, vegetables, fish, olive oil, and moderate wine consumption, offers protective benefits.

Adopting a healthier lifestyle that includes regular physical activity, a balanced diet, and avoiding smoking can significantly reduce the risk of prostate cancer.

SUGGESTED READINGS

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Aquablation vs. Laser Surgery for BPH: New Findings from the EAU25 Congress

EAU25 Press Release: Waterjet surgery for an enlarged prostate can offer relief, without compromising sexual enjoyment (<https://eaucongress.uroweb.org/eau25-press-release-waterjet-surgery-for-an-enlarged-prostate-can-offer-relief-without-compromising-sexual-enjoyment/>)

The EAU25, Europe's largest urology congress, took place in Madrid, Spain, from March 21-24, 2025. Among the key topics discussed was the latest research on Benign Prostatic Hyperplasia (BPH), a common condition in aging men that affects over 50% of those over 50 and more than 80% over 70. While non-cancerous, BPH can lead to significant urinary issues.

BPH occurs when the prostate gland enlarges, compressing the urethra and causing symptoms such as frequent urination, weak urine stream, and leakage. When medication or lifestyle changes fail, surgical options like laser therapy or wire-loop resection are considered. However, retrograde ejaculation is a common side effect of these procedures.

A major highlight of the congress was the **WATER III trial**, which compared **Aquablation**, a robotic water-jet treatment, with standard laser surgeries (**HoLEP** and **ThuLEP**) for men with large prostates (80–180 mL). In the trial, the researchers recruited 202 men who required surgery for their BPH. Just over half (98) of patients were assigned to undergo aquablation therapy, with the remainder (88) assigned to undergo either HoLEP or ThuLEP laser surgery. Conducted across Germany

and the UK, the study involved 202 patients, assessing their recovery and side effects over three months.

Lead researcher **Professor Manuel Ritter** (University Hospital Bonn) noted that **Aquablation preserved ejaculatory function while effectively treating symptoms**, making it a promising alternative. **Professor Cosimo De Nunzio** (Sapienza University, Rome) emphasized the need for **longer follow-ups** to confirm the procedure's long-term benefits.

These findings offer new hope for men seeking effective BPH treatment while maintaining sexual function.



