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Rheumatoid arthritis is an autoimmune disease triggered by *Proteus* urinary tract infection

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Abstract

Rheumatoid arthritis (RA) is a chronic and disabling polyarthritic disease, which affects mainly women in middle and old age.

Extensive evidence based on the results of various microbial, immunological and molecular studies from different parts of the world, shows that a strong link exists between *Proteus mirabilis* microbes and RA. We propose that sub-clinical *Proteus* urinary tract infections are the main triggering factors and that the presence of molecular mimicry and cross-reactivity between these bacteria and RA-targeted tissue antigens assists in the perpetuation of the disease process through production of cytopathic auto-antibodies.

Patients with RA especially during the early stages of the disease could benefit from *Proteus* anti-bacterial measures involving the use of antibiotics, vegetarian diets and high intake of water and fruit juices such as cranberry juice in addition to the currently employed treatments.

Keywords: *Humoral autoimmunity,* Proteus mirabilis*, rheumatoid arthritis, urinary tract infection*

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease, which affects millions of people all around the world, with a prevalence rate ranging from 0.5 to 1% (Lawrence et al. 1998). The disease in the majority of patients takes a mild to moderate course, whilst in others it has a more disabling consequence, which might have a great effect on the socio-economic status of the patient (Cooper 2000).

RA affects individuals of middle age groups and occurs three times more frequently in women than in men.

Aetiopathogenesis

A general scientific consensus exists, which considers RA as an immune-mediated disease that could possibly be triggered by an environmental (microbial) factor in a genetically susceptible individual.

Extensive evidence supports the role of cellular and humoral autoimmunity in the development of RA, and some of these are listed as follows:

1. Predominant role of B lymphocytes in the pathogenesis of RA (Weyand et al. 2005) and signs of accumulations of immunoglobulins and other inflammatory products such as complements at the site of synovial pathological lesions in RA patients (Low and Moore 2005).
2. Detection of elevated levels of auto-antibodies in the serum and/or synovial fluid of patients with RA (Rantapaa-Dahlqvist 2005).
3. Significant improvements in RA disease parameters following B cell depletion therapy, e.g. with the use of anti-CD20 antibodies (Perosa et al. 2005).

Role of HLA genes in RA

The role of genetics in development of RA has been examined mainly through family, twin and molecular analytical studies. For instance, familial distribution of RA among first-degree relatives (Deighton et al. 1992a) and twins (MacGregor et al. 2000), indicates that RA runs in some families, basically supporting the

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concept of a genetic contribution, but at the same time arguing against the proposition that RA could be considered as a purely genetic disorder. However, in two separate genome-wide screenings with affected sib pairs, it has been shown that HLA haplotypes had the largest genetic contribution in RA (Cornelis et al. 1998; Jawaheer et al. 2001).

Nearly three decades ago, HLA-DR4 was the first genetic marker among other class II molecules, found to be significantly liked with RA susceptibility (Stastny 1976). It has been shown later that various other HLA-DRB1 alleles were either associated (HLA-DRB*0101, *0102, *0401, *0404, *0405, *1001 and 1402) or not associated (HLA-DRB*0103, *0402, *0403 and *0408) with RA (Newton et al. 2004), based on certain differences occurring within amino acid sequences at the location 69–74 "EQRRAA" which has been termed as the "shared epitope" (SE) moiety (Gregersen et al. 1987).

Regardless of the difference in the distribution of HLA genes among various ethnic groups, it has been reported that more than 95% of patients possess at least one of the RA-linked HLA-DR molecules (Weyand et al. 1992), which contain the "SE" amino acid sequence. Further to its role in conferring the disease susceptibility, these RA-associated HLA-DRB1 alleles have also been reported to have a great impact on the disease severity and extra-articular manifestations in patients with RA (Turesson et al. 2005).

Immunological and molecular links between RA and Proteus

During the last 3 decades an extensive literature on the link between *Proteus* microbes and RA has been published in peer-reviewed journals. These studies were carried out by various independent groups worldwide. Some of this evidence, listed in chronological orders, can be summarized as follows: (Table I)

1. In early 1970s, a group from Tennessee reported an increase in the geometric mean titres of antibodies to *Proteus* OXK and herpes virus hominis but not to 28 other infectious disease antigens in RA patients when compared to controls (Chandler et al. 1971).
2. In mid 1980s, our group reported for the first time that antibody levels against *P. mirabilis*, a urinary pathogen, were significantly elevated in RA patients when compared to those with ankylosing spondylitis (AS) or healthy control subjects (Ebringer et al. 1985).
3. In early 1990s, we have identified an amino acid sequence homology between the "EQ/KRRAA" amino acid motif present in RA HLA-susceptibility molecules and the "ESRRAL" sequence present in *P. mirabilis* haemolysins (Ebringer et al. 1992).
4. In mid 1990s, our group has found another molecular homology between "LRREI" amino acid sequence present in type XI collagen and "IRRET" amino acid motif present in *Proteus* urease enzymes (Wilson et al. 1995).
5. In late 1990s, *in vitro* and *in vivo* immunological cross reactivities have been observed between synthetic peptides from *Proteus* haemolysin and urease enzyme molecules and those of HLA-DR1/DR4 and collagen self-antigens (Tiwana et al. 1999). Furthermore, Senior and colleagues from Dundee, have found that *Proteus mirabilis* is the most prominent microbe encountered in the urine of RA patients, who had bacteriuria more frequently than age- and sex-matched healthy controls (Senior et al. 1999).
6. In the year 2003, our group has shown that anti-ESRRAL *Proteus* antibodies from patients with active RA can haemolyse sheep red blood cells (SRBC) coated with HLA-DR4/1-containing "EQRRAA" but not HLA-B27-containing "QTDRED" amino acid synthetic peptides more frequently than patients with AS and healthy controls. By contrast, active AS patients with high anti-QTDRED *Klebsiella* antibodies had higher levels of an *in vitro* haemolytic reactions on SRBCs coated with "QTDRED" but not "ESRRAL" synthetic peptides when compared to patients with RA or to healthy controls (Wilson et al. 2003). Hence, RA and AS groups of patients could behave as reciprocal controls to each other concerning the involvement of antibodies against *Proteus* antigens in RA and *Klebsiella* antigens in AS. Blood donors did not react against either *Proteus* or *Klebsiella* antigens.
7. Between the year 1985 and 2003, many serological studies have been carried out by various independent groups. Cumulatively, they show that elevated antibodies against various antigens from *Proteus mirabilis* were observed in more than 1350 RA patients from 15 different countries worldwide when compared to corresponding healthy controls (Ebringer et al. 2003).
8. In the year 2004, a collaborative study was carried out involving Finish and Japanese patients with RA. It was observed that these patients were all showing significantly elevated levels of IgG antibodies to whole and synthetic peptide antigen preparations from *P. mirabilis* but not to those from *E. coli* and *S. marcescens* bacteria when compared to corresponding healthy controls or patients with systemic lupus erythematosus (Rashid et al. 2004).
9. In a recent multi-centre prospective study, it has been shown that rheumatoid factor-(RF) positive patients with RA had significantly elevated levels of IgM and IgA antibodies against *Proteus mirabilis* and IgA antibodies against *E. coli* when compared to disease and healthy control subjects

Table I. Chronologically listed evidence of microbiological, molecular and immunological links between *Proteus* microbes and rheumatoid arthritis

Reference	Basic results	Methods used
Chandler et al. (1971)	Elevated antibodies to *Proteus* OXK and herpes virus but not to 22 other microbial agents in RA patients when compared HCs.	Direct agglutination assay
Ebringer et al. (1985)	Elevated antibodies to *P. mirabilis* but not *Klebsiella* microbes in patients with RA when compared to AS patients and HCs.	Indirect agglutination assay
Abuljadayel et al. (1988)	Elevated anti-*Proteus* antibodies in RA patients compared to HCs.	IIF
Rogers et al. (1988)	Elevated levels of anti-*Proteus* antibodies in RA patients compared to other disease or healthy controls.	ELISA
Nasonova et al. (1989)	Increased anti-*Proteus* antibodies in the majority of Russian RA patients when compared to corresponding disease or healthy controls.	ELISA
Wilson et al. (1990)	Increased isolation of *P. mirabilis* from urine of RA patients when compared to patients with OA or to HCs.	CLED (Oxoid Ltd) growth and API20E (bioMerieux, Inc) identification methods
Deighton et al. (1992b)	Absence of positive correlations between elevated antibodies to *P. mirabilis* and antibodies against 4 viruses and 8 auto-antigens in patients with RA when compared to HCs	IIF
Ebringer et al. (1992)	Molecular homology between *Proteus* haemolysins and HLA-DR4/1 antigens.	SwissProt and GenBank database search
Ebringer et al. (1993)	Increased isolation rate of *P. mirabilis* from urine of female more than male patients with RA and in RA patients as a whole when compared to healthy subjects.	CLED growth and API20E (bioMerieux, Inc) identification methods
Fielder et al. (1995)	Elevated antibodies to *P. mirabilis* but not to *E. coli* or *S. Typhi* bacteria in French patients with RA when compared to corresponding HCs.	ELISA and IIF
Subair et al. (1995)	Elevated antibodies to *P. mirabilis* but not to *E. coli* or other normal bowel microbial inhabitants in Bermudian patients with RA when compared to corresponding HCs.	ELISA and IIF
Wilson et al. (1995)	Molecular similarities between *Proteus* urease and collagen type XI antigens. Elevated antibodies to *Proteus* haemolysin and urease as well as to HLA-DR4/1 and collagen antigenic peptides.	SwissProt and GenBank database search and ELISA
Tiwana et al. (1996)	Elevated antibodies to *Proteus* but not to *Serratia*, *Escherichia* and *Pseudomonas* bacteria in RA patients when compared to HCs.	ELISA
Wanchu et al. (1997)	Elevated antibodies to *P. mirabilis* but not to *S. typhi* in Indian patients with RA when compared to OA patients and to HCs.	Tube agglutination
Wilson et al. (1997)	A positive correlation between high serum anti-*Proteus* antibody levels and urine *Proteus* isolation rates in patients with RA.	ELISA and API20E methods
Blankenberg-Sprenkels et al. (1998)	Elevated anti-*Proteus* but not anti-*Klebsiella* antibodies in Dutch RA patients when compared to patients with AS or to HCs.	IIF
Tiwana et al. (1999)	In vitro and in vivo immunological cross-reactivities between antibodies against *P. mirabilis* and self-antigenic peptide molecules.	ELISA and peptide binding dilution assay
Rashid et al. (1999)	Elevated antibodies to *P. mirabilis* in Spanish and Norwegian patients with RA when compared to corresponding HCs.	IIF

Table I – *continued*

Reference	Basic results	Methods used
Senior et al. (1999)	Sub clinical *Proteus* bacteriuria and elevated levels of anti-*Proteus* antibodies in urine and serum of patients with RA when compared to HCs.	ELISA and Immunoblot
Ushakova et al. (2000)	Elevated IgM and IgG antibodies to *P. mirabilis* in Russian patients with RA when compared to HCs.	ELISA
Wilson et al. (2003)	In vitro immunological cytotoxicity reaction occurring between anti-*Proteus* and anti-HLA-DRB1 antibodies with the corresponding crossreactive peptide molecules.	ELISA and sheep red cell haemolytic assays
Rashid et al. (2004)	Finish and Japanese patients with RA had elevated antibodies against whole and synthetic peptide antigenic preparations from *P. mirabilis* but not those from *E. coli* and *S. marcescens* when compared to corresponding HCs.	ELISA and IIF
Newkirk et al. (2005)	Elevated IgM and IgA antibodies to *P. mirabilis* and IgA antibodies to *E. coli* but not to 6 other bacterial and viral agents in rheumatoid factor positive RA patients when compared to those with other rheumatic diseases.	ELISA

ELISA = Enzyme linked immunosorbent assay; HCs = Healthy controls; IIF = Indirect immunofluorescence; RA = Rheumatoid arthritis; AS = Ankylosing spondylitis; OA = Osteoarthritis; CLED = Cystine lactose-electrolyte deficient.

(Newkirk et al. 2005). However, many other studies carried out previously had shown that only anti-*Proteus* but no anti-*E. coli* antibodies were observed to be elevated in RA patients (Fielder et al. 1995, Subair et al. 1995; Tiwana et al. 1996; Tani et al. 1997; Rashid et al. 2004).

10. In another study carried out by a group from Los Angeles, RA patients were reported to have IgA anti-*Proteus* antibodies detectable more than in healthy controls. However, several molecules from this microbe had shown reduced IgA immune responses compared to controls (Weisbart et al. 2005). It has been suggested that the occurrence of some "holes" in the IgA immune repertoire for certain antigens in *Proteus* bacteria could explain the possibility that RA patients are more liable to harbour this microbe and to have more frequent bouts of (albeit, sub-clinical) infections, with a consequent intermittent and/or progressive enhancement of anti-*Proteus* antibody responses.
11. Most recently, our group has studied the humoral immune responses against a new antigenic moiety from *Proteus* urease F enzyme, which was found to be non homologous to RA-targeted synovial tissue structures. We have shown that active RA patients had significantly elevated IgG and IgM anti-*Proteus* peptide antibodies when compared to healthy controls (Rashid et al. submitted). This latter finding argues against the suggestion that elevated antibodies against the *Proteus* crossreactive antigens in RA patients could be an epiphenomenona resulting from increased exposure of auto-antigens due to pathological damages produced by bacterial triggers.

Proteus *urinary tract infections and RA*

Various microbiological and immunological data results support the suggestion that there is a link between RA and urinary tract infections (UTI) mainly caused by *Proteus* (Table II).

Patients with RA were reported to have a higher frequency of recurrent UTIs (Lawson and Maclean 1966; Tishler et al. 1992). Urine samples from RA patients yield higher isolation rates of *P. mirabilis* microbes than patients with osteoarthritis or healthy controls (Ebringer et al. 1993). RA patients had higher levels of antibodies against *Proteus* in their urine when compared to those of healthy subjects (Senior et al. 1999) and significant correlation was detected between serum anti-*Proteus* antibodies and *Proteus* urinary isolation rates in RA patients when compared to healthy controls (Wilson et al. 1997). Furthermore, RA patients group who were receiving a vegetarian diet had a drop in the levels of antibodies against *P. mirabilis* but not *E. coli*, when compared to those patients who were omnivores (Kjeldsen-Kragh et al. 1995). This dietary treatment may have exerted its specific anti-microbial effect via the actions of lignans and phytoestrogen metabolites (Adlercreutz et al.

Table II. Direct and indirect evidence of the links between *Proteus* UTIs and RA

Direct evidence:

1) *Proteus mirabilis* bacteria were isolated more frequently in patients with RA than those with other disease and healthy controls (Wilson et al. 1990; Senior et al. 1999).
2) A positive correlation has been detected between anti-*Proteus* antibodies and the rate of isolation of these microbes from urine of RA patients when compared to healthy subjects (Wilson et al. 1997).
3) RA patients receiving vegetarian diet are more liable to have decreased levels of anti-*Proteus* antibodies than omnivores (Kjeldsen-Kragh et al. 1995).
4) Elevated levels of anti-*Proteus* antibodies were observed in sera of RA patients coming from 15 different countries (Ebringer et al. 2003).

Indirect evidence:

1) Patients with severe RA had a higher frequency of recurrent UTIs (Tishler et al. 1992).
2) Women are more liable to develop recurrent UTIs (Franco 2005). This finding in combination to point number 1 above, could explain why RA is more common among women than men.
3) *Proteus* bacteria, which are urease-positive, account for 15% of UTIs, and affect the upper urinary tract, especially kidneys, whilst *E. coli*, another urogenic but urease-negative bacteria, account for the majority of UTIs and mainly involve bladder (Cattell 2005).
4) Patients with recurrent UTIs are more likely to respond to high daily intake of cranberry juice (Raz et al. 2004). Whether cranberry juice could have a beneficial effect in patients with RA needs to be investigated in a prospective controlled study.

1986), which are known to possess anti-bacterial activity *in vitro* (Ito et al. 1982).

Females are more vulnerable to develop UTIs than males and up to 60% of women have been reported to develop at least one episode of UTI in their lifetime (Foxman et al. 2000). A significant number of these women might have recurrent infections, and the chance of infection by *Proteus* species was found to increase with age (Nicolle 1996).

The increased incidence of UTIs in RA patients and the more frequent occurrence of UTIs in females, especially those of middle age and elderly groups might give an answer to the higher prevalence of RA among women.

Molecular mimicry as a plausible aetiopathogenetic mechanism

Molecular and immunological inter-relation between the triggering aetiological factor, namely *Proteus mirabilis* antigens, and targeted synovial tissue structures expressing HLA molecules that contain "SE" amino acid motif and collagen type XI, in RA could be explained by the molecular mimicry or cross-reactivity mechanism (Ebringer et al. 2005). High antibody titres against *Proteus* haemolysin and urease antigens in patients with active RA could bind to cross-reactive self antigens and consequently result in production of various inflammatory and immunological damaging mediators based on the mechanism of antibody-mediated cytotoxicity reactions (Figure 1). Damage to the synovial and other joint structures could result in the release of self-antigenic particles and auto-antibody production. Anti-*Proteus* cross-reactive antibodies, which might result from recurrent, albeit subclinical UTIs, together with high levels of secondary auto-antibodies will bind to RA-targeted antigens in the synovial tissues. These immunological reactions could coincide with the initiation of clinical and laboratory exacerbations and further pathological damages.

Proposal of a new therapeutic strategy

Currently patients with RA are treated with various therapeutic strategies involving the use of anti-inflammatory, immunosuppressive and biological agents as well as non-medical treatment modalities (Genovese and Harris 2005).

Although, the current medical treatments, especially those involving anti-tumour necrosis factor therapies (Haraoui 2005), have a promising beneficial effect particularly in easing or even halting the disease progress, they are expensive (Merkesdal et al. 2004) and cause side-effects. In order, to achieve a prolonged clinical remission, continuous immuno-suppression with these drugs is required because this kind of treatment could not eradicate the causative microbial agents.

Based on the existing evidence for involving *Proteus* bacteria in the pathogenesis of RA, it is logical to propose a new therapeutic modality in the management of RA, which could be implemented in conjunction with other currently used treatments. This new treatment includes anti-*Proteus* measures involving the use of *Proteus*-sensitive antibiotics with dietary manipulations in the forms of vegetarian diet (Kjeldsen-Kragh et al. 1995) and high daily intake of water and fruit juices containing fructose such as cranberry juice (Rashid et al. 2001).

It could also be possible to make a vaccine mainly derived from *Proteus* antigenic molecules that do not contain the cross-reactive epitopes, in order to prevent susceptible individuals of acquiring *Proteus* UTIs and decrease the chance of developing RA or at least limit further damages in those with established disease.

Conclusion

Based on the results of various studies carried out in relation to *Proteus* microbes, it could be said that compelling evidence exists linking this microbe to RA, starting with recurrent sub-clinical *Proteus* UTIs and ending in the full development of RA. To prove the scientific logic of this possibility, and its benefit to patients clinical trials using anti-*Proteus* measures in RA are required to be carried out in prospective longitudinal studies.

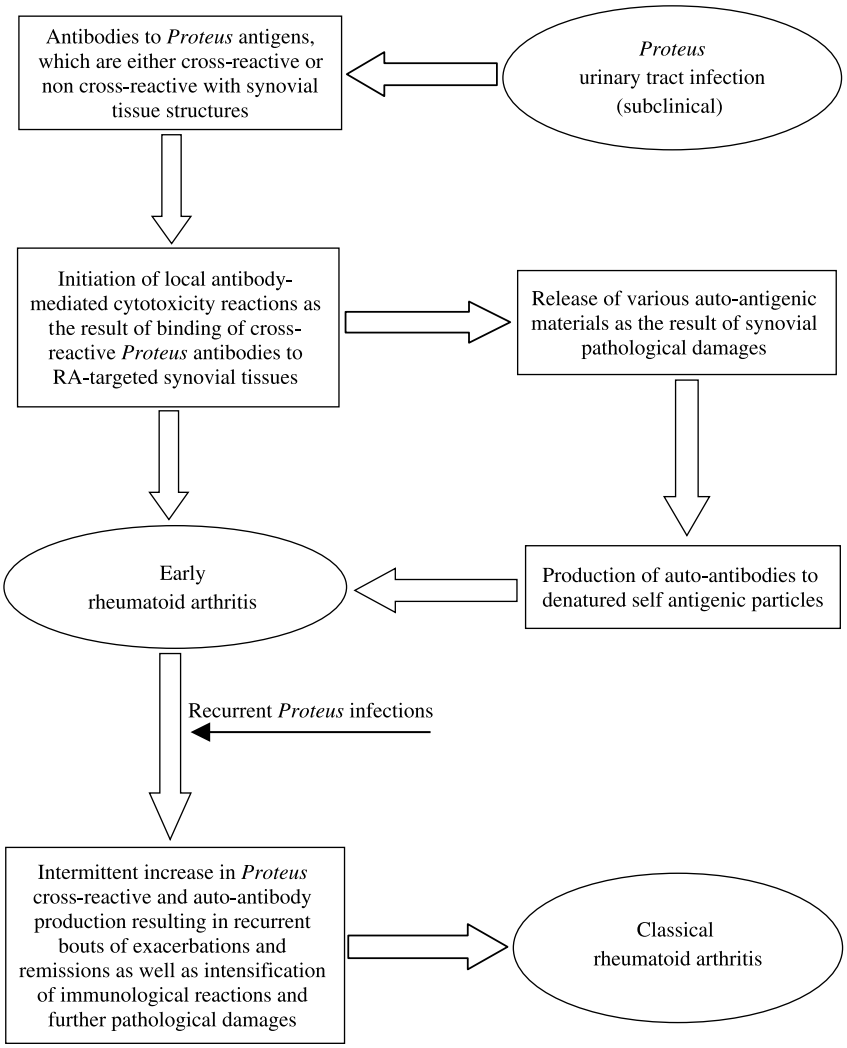

Figure 1. Schematic representation of pathological steps in the development of rheumatoid arthritis.

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Interdisciplinary Perspectives on Infectious Diseases

Special Issue on Climate Change and Infectious Disease

Call for Papers

Virtually every atmospheric scientist agrees that climate change—most of it anthropegenic—is occurring rapidly. This includes, but is not limited to, global warming. Other variables include changes in rainfall, weather-related natural hazards, and humidity. The Intergovernmental Panel on Climate Change (IPCC) issued a major report earlier this year establishing, without a doubt, that global warming is occurring, and that it is due to human activities.

Beginning about two decades ago, scientists began studying (and speculating) how global warming might affect the distribution of infectious disease, with almost total emphasis on vector-borne diseases. Much of the speculation was based upon the prediction that if mean temperatures increase over time with greater distance from the equator, there would be a northward and southward movement of vectors, and therefore the prevalence of vector-borne diseases would increase in temperate zones. The reality has been more elusive, and predictive epidemiology has not yet allowed us to come to conclusive predictions that have been tested concerning the relationship between climate change and infectious disease. The impact of climate change on infectious disease is not limited to vector-borne disease, or to infections directly impacting human health. Climate change may affect patterns of disease among plants and animals, impacting the human food supply, or indirectly affecting human disease patterns as the host range for disease reservoirs change.

In this special issue, Interdisciplinary Perspectives on Infectious Diseases is soliciting cross-cutting, interdisciplinary articles that take new and broad perspectives ranging from what we might learn from previous climate changes on disease spread to integrating evolutionary and ecologic theory with epidemiologic evidence in order to identify key areas for study in order to predict the impact of ongoing climate change on the spread of infectious diseases. We especially encourage papers addressing broad questions like the following. How do the dynamics of the drivers of climate change affect downstream patterns of disease in human, other animals, and plants? Is climate change an evolutionary pressure for pathogens? Can climate change and infectious disease be integrated in a systems framework? What are the relationships between climate change at the macro level and microbes at the micro level?

Authors should follow the Interdisciplinary Perspectives on Infectious Diseases manuscript format described at the journal site http://www.hindawi.com/journals/ipid/. Prospective authors should submit an electronic copy of their complete manuscript through the journal Manuscript Tracking System at http://mts.hindawi.com/, according to the following timetable:

Manuscript Due	June 1, 2008
First Round of Reviews	September 1, 2008
Publication Date	December 1, 2008

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Advances in Urology

Special Issue on Practice Management and Health Policy

Call for Papers

The explosion of better health care technology coupled with the government's inability to adequately pay for these services has caused a major dilemma. Because of this, many different reimbursement paradigms have been suggested to replace the current fee for service system. This movement in part also stems from the Institute of Medicine's (IOM) 1998 report "To Err is Human" which reported that approximately 98 000 people die annually in the United States because of preventable medical mistakes. This has raised public awareness of medical errors and sparked new ideas from payers and consumers in order to improve health care quality and outcomes. In 2001, the IOM's subsequent report recommended aligning reimbursement policies with quality improvement thus increasing awareness of pay-for-performance (P4P), a reimbursement system based on rewarding physicians for the quality, rather than quantity, of provided care. With P4P initiatives currently underway in both the private and public sectors, there has been increased attention towards refining healthcare delivery through improved efficiency, application of core business principles to ambulatory care, and improving patient satisfaction.

The scope of this special edition is two fold: one is to focus on the importance of practice management and to present and discuss research in this area along with commentary on the implementation of electronic medical records, practice mergers, and methods to improve practice efficiency. The second objective is to provide the reader with health policy updates from nationally recognized experts and organizations regarding many of the rapidly evolving issues involving urologists.

The list of topics to be covered includes, but is not limited to:

- Office efficiency in the urology practice
- The impact of physician work effort both in the operating room and in the office: what is the best balance?
- Merging physician practices: lessons learned
- Update from MEDPAC on current health policy trends as related to reimbursement in the United States (Ron Castellanos)
- Leverage advocacy: promoting new models for health policy in urology (UROPAC: Sam Sheppard)
- The ramifications of the pay for performance reimbursement paradigm on clinical practice patterns for common urologic conditions
- The impact of electronic medical records on physician practice
- Update on AUA efforts in the area of physician quality reporting and the development of urology specific quality measures

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Advances in Urology

Special Issue on Postradical Prostatectomy Rehabilitation Therapy

Call for Papers

The use of oral type-V phosphodiesterase inhibitors has been increasingly common over the last several years for the purposes of penile rehabilitation. This edition will provide a current assessment of the evidence supporting this practice. The concerns regarding the true benefit of penile rehabilitation will also be examined.

Topics of interest include, but are not limited to:

- Basic science evidence for the benefits of penile rehabilitation therapy
- Overview of penile rehabilitation therapy
- An appraisal of the peer-reviewed clinical literature on penile rehabilitation therapy
- Experience with penile rehabilitation therapy after robot-assisted laparoscopic prostatectomy

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Interdisciplinary Perspectives on Infectious Diseases

Special Issue on
The Human Microbiome and Infectious Diseases: Beyond Koch

Call for Papers

A century after Robert Koch linked individual cultured microbes to specific diseases (Koch's postulates), it is increasingly apparent that the complex community of microorganisms associated with the human body (the "microbiome") plays a key role in health and disease. The National Institute of Health (NIH) recently announced the Human Microbiome Project and among its goals is to understand the relationship between host-associated microbial communities and disease. Many physicians and researchers, however, have only passing familiarity with the concepts involved in the study and therapeutic manipulation of complex microbial communities. The aims of this special issue are (1) to familiarize the readers with the concepts and methods for the study of complex microbial communities, (2) to demonstrate how changes in the indigenous microbial community can play a role in diseases such as antibiotic-associated diarrhea, bacterial vaginosis, and cystic fibrosis, and (3) to review how probiotics may hold promise for the therapeutic manipulation of the indigenous microbiota. Review articles and original research papers are being sought for this special issue.

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Guest Editors

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Advances in Urology

Special Issue on
Comprehensive Management of Upper Tract Urothelial Carcinoma

Call for Papers

Urothelial carcinoma of the upper urinary tract is relatively uncommon, representing only 5% of all urothelial cancers. The 5-year cancer-specific survival for upper tract urothelial carcinoma in the United States is roughly 75% with grade and stage serving as the most powerful predictors of survival. Nephroureterectomy with excision of the ipsilateral ureteral orifice and bladder cuff en bloc remains the gold standard treatment for upper tract urothelial carcinoma, but endoscopic and laparoscopic approaches, are rapidly evolving as standards of care depending on grade and stage of disease. Several controversies remain in management of upper tract urothelial carcinoma including patient selection for endoscopic versus laparoscopic approaches, management strategies of the distal ureter, the role of lymphadenectomy in upper tract urothelial carcinoma, and the value of chemotherapy in upper tract disease.

Aims of this special edition will be to critically review and evaluate controversies in management of upper tract urothelial cancer including: endoscopic management of upper tract urothelial carcinoma, laparoscopic nephroureterectomy and management of the distal ureter, the role of lymphadenectomy in management of upper tract urothelial cancer, and the emerging role of chemotherapy in upper tract disease.

- Endoscopic management of upper tract urothelial carcinoma
- Laparoscopic nephroureterectomy and management of the distal ureter
- Role of lymphadenectomy in management of upper tract urothelial cancer
- Role of chemotherapy in management of upper tract urothelial carcinoma

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Advances in Urology

Special Issue on
The Changing Concepts of Vesicoureteral Reflux in Children

Call for Papers

Vesicoureteral reflux (VUR) is considered an enigma of pediatric urology practice, where the management of this salient disease evolved from surgical intervention to observation. Bladder physiology and dysfunction has become the culprit behind VUR, making the diagnosis of primary reflux a historical diagnosis. However, recently the introduction of Deflux and other injectable materials revolutionized the management of VUR in pediatric population. Subsequently, from the moment a child is diagnosed with reflux, pediatric urologists are faced with challenging questions both by parents and peers:

- Do antibiotics have a role in management of VUR?
- If the management of reflux is conservative, do we really need to have this pathology diagnozed? and which radiological modality is better?
- What are the current surgical modalities to treat reflux in 2008?
- What if reflux is not treated, does it cause higher risk of infections in girls at puberty?
- What can the literature tell us? More specifically, do we have enough objective data in the literature on the research and outcome of VUR that will help pediatric urologists make a decision?

Voiding cystourethrogram is recognized as a disturbingly invasive test in pediatrics and sedation, for this test is becoming a routine for children undergoing this test in some centers.

This special issue on the changing concepts of vesicoureteral reflux in children will be focused on addressing most of these questions in an attempt to provide a state-of-the-art foundation for decision making when a urologist is faced with a child who harbors VUR.

The ideal list of topics to be covered is as follows:

- Bladder dynamics, voiding dysfunction and reflux
- Endoscopic treatment: technique
- Intravesical ureteral reimplantation: surgical technique
- Extravesical ureteral reimplantation: surgical technique
- Antibiotics and vesicoureteral reflux
- Diagnostic approach to reflux in 2007
- Outcome of surgical versus medical management of VUR
- Update on reflux nephropathy and ESRD 2nd to VUR
- Relation between Deflux volume and reflux resolution
- Reflux treatment evolution
- Design of study
- VCUG and radiation
- Sedation and VCUG
- Reflux and puberty
- VUR management: state of the art or state of confusion

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