

# Is There a Role for Helicobacter Pylori Infection in Urological Diseases?

Mohammed S Al-Marhoon

**Introduction:** *Helicobacter pylori* (*H pylori*) infection is a focus of attention nowadays. It has been found to cause gastrointestinal disorders and also extra-intestinal disorders. The aim of this paper is to explore the role of *H pylori* in urological diseases and to keep urologists up to date in this subject.

**Materials and Methods:** Medline and PubMed were searched from 1950 to December 2007 for the following combined terms: *Helicobacter pylori* together with *urology, urological diseases, kidney, kidney cancer, ureter, bladder, bladder cancer, prostate, prostate cancer, benign prostatic hyperplasia, urethra, seminal vesicle, testis, and testicular cancer.*

**Results:** Accumulating evidence is appearing in the literature relating *H pylori* infection to urological diseases. The most obvious is the implication of *H pylori* in inducing chronic cystitis leading to bladder lymphoma. In addition, some epidemiological studies have shown significant associations between infective chronic prostatitis and prostatic carcinoma.

**Conclusion:** A simple hypothetical model relating *H pylori* infection to prostate and bladder diseases is proposed to stimulate the collaborative work between the urologists and scientists to explore this field which is underinvestigated to date. If *H pylori* is found to have a significant role in urological diseases, prevention of bladder and prostate cancers by eradication of *H pylori* infection may become a reality like what happened in the treatment of peptic ulcer disease and gastric cancer.

Keywords: *Helicobacter pylori*, prostatic neoplasms, urinary bladder neoplasms, lymphoma, prostatitis

Urol J. 2008;5:139-43.  
www.uj.unrc.ir

## INTRODUCTION

Today, *Helicobacter pylori* (*H pylori*) infection is a focus of attention. It has been found to cause gastrointestinal disorders and extra-intestinal disorders, too. The gastrointestinal disorders include gastric adenocarcinoma, gastric lymphoma, duodenal ulcer, and chronic atrophic gastritis.<sup>(1-4)</sup> Whereas, the extra-intestinal disorders include vascular, respiratory, liver, skin, and kidney diseases.<sup>(5-9)</sup>

The possibility that a bacterium could cause gastritis, peptic ulcer, and cancer was a difficult concept

to accept, especially as it would change the whole concept of the pathophysiology of ulcer disease which was based on acid etiology. It is now clear that infection with *H pylori* is associated with peptic ulcer disease and gastric cancer. *Helicobacter pylori* has been designated a group 1 (definitive) carcinogen by the World Health Organization.<sup>(10)</sup> The pathways by which *H pylori* leads to gastric cancer have been shown by models of gastric carcinogenesis. Correa's multistep model<sup>(11)</sup> showed that *H pylori* infection is a triggering

Department of Urology, Mansoura University, Urology and Nephrology Center, Mansoura, Egypt

Corresponding Author:  
Mohammed S Al-Marhoon, PhD,  
MRCSEd, MD, BSc  
Department of Urology, Mansoura University, Urology and Nephrology Center, Mansoura, Egypt  
Tel: +20 16 670 7732  
Fax: +20 50 226 3717  
E-mail: almarhoon@hotmail.com

factor in the process of increasingly severe gastric lesions progressing from chronic active gastritis to atrophy, intestinal metaplasia, dysplasia, and gastric cancer. Earlier, we proposed a model indicating the initial changes induced by *H pylori* infection that play a role in protecting the organism and enhancing its colonization in the stomach that may lead to gastric cancer.<sup>(12)</sup> The aim of this paper is to explore the role of *H pylori* in urological diseases through a review of published articles and to keep the urologists up to date on this subject. New discoveries about the role of bacteria in urological neoplasms and other diseases may change the concepts of treatment in urology like what happened in the treatment of peptic ulcer disease and gastric cancer.

## MATERIALS AND METHODS

Medline and PubMed were searched from 1950 to December 2007 for the following combined terms: *Helicobacter pylori* together with *urology*, *urological diseases*, *kidney*, *kidney cancer*, *ureter*, *bladder*, *bladder cancer*, *prostate*, *prostate cancer*, *benign prostatic hyperplasia*, *urethra*, *seminal vesicle*, *testis*, and *testicular cancer*. A total of 124 articles were found, of which 27 that were relevant to our subject were reviewed. There were 6, 16, and 5 articles on *H pylori* related to the kidneys, bladder, and prostate, respectively. No title was found on the subject in relation to the ureters, seminal vesicles, urethra, or testes.

## HELICOBACTER PYLORI

*Helicobacter pylori* is a spiral gram-negative rod. It has 2 important strains based on their genetic characteristics: vacuolating toxin gene (*vacA*) and cytotoxin associated gene (*cagA*). The *cagA* strains are more virulent than *vacA* strains.<sup>(13)</sup> *Helicobacter pylori* infection triggers local and systemic inflammatory response. It may cause chronic inflammation and stimulate chronic systemic inflammatory response through the production of various inflammatory metabolites, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (IFN- $\gamma$ ), interleukin 1 $\beta$  (IL-1 $\beta$ ), interleukin 6 (IL-6), interleukin 8 (IL-8), and interleukin 10 (IL-10).<sup>(14,15)</sup> These mechanisms and the latest findings on *H pylori* infection and its

relation with urinary tract and urological diseases are discussed below.

## Prostatitis

It has long been known that certain infectious agents that affect specific areas of the body can also have systemic sequelae. A typical example of this is infection with beta-hemolytic *Streptococcus* group A. These bacteria frequently cause acute or chronic tonsillitis, which can also lead to glomerulonephritis. *Helicobacter pylori* might also be a cause of infections distant from the stomach. Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most common form of the prostatitis syndromes.<sup>(16)</sup> The etiology of CP/CPPS is unknown in most of the cases, although some of the microorganisms including *Escherichia coli*, *Mycoplasma genitalium*, or *Chlamydia trachomatis* are accused as the etiology of CP/CPPS.<sup>(17)</sup> Chronic prostatitis might have been triggered by secondary inflammatory reactions to an unknown antigen. In CP/CPPS, no organism could be exactly found by conventional methods of microbiology. There are many measurable proinflammatory cytokines and chemokines in human semen such as IL-1 $\beta$ , IL-6, IL-8, IL-10, IFN- $\gamma$ , and TNF- $\alpha$  that show high levels in seminal, plasma, and/or expressed prostatic secretion of men with CP/CPPS.<sup>(18)</sup> One could hypothesize that chronic infection with *H pylori* may be an occult etiological factor in the pathogenesis of CP/CPPS by inducing the secretion of IL-1 $\beta$ , IL-6, IL-8, IL-10, IFN- $\gamma$ , and TNF- $\alpha$ . Thus, finding a relationship between *H pylori* infection and chronic prostatitis may help in finding new approaches for the diagnosis and treatment of CP/CPPS.

It has been demonstrated that the prostate does not harbor normal bacterial flora by the absence of bacterial genomes in histologically normal prostates.<sup>(19)</sup> The etiology of the chronic prostatitis/pelvic pain syndrome remains controversial, some believing that bacteria are present but do not appear on conventional aerobic cultures. A molecular technique to detect bacteria that do not grow in such cultures is to use polymerase chain reaction assay for bacterial 16S rDNA. Bacterial DNA sequences were

found to be present in prostate biopsy specimens in 77% of men with chronic prostatitis/pelvic pain syndrome.<sup>(20)</sup> Also, 78% of prostatectomy specimens from men who had prostate cancer or benign prostatic hyperplasia (BPH) were positive for bacterial DNA.<sup>(19)</sup>

### Prostate Cancer

In 1999, a case of the association of prostatic adenocarcinoma with adenocarcinoid of the ileum and gastric mucosa-associated lymphoid tissue (MALT) lymphoma with *H pylori* infection was reported in the literature.<sup>(21)</sup> Carcinoma of the prostate is the most frequently diagnosed malignancy of men in the western countries.<sup>(22)</sup> It has been hypothesized that prostatic infection and inflammation might be a cause of prostatic carcinoma. Epidemiological studies show significant associations between infection and prostatic carcinoma.<sup>(23,24)</sup> Proliferative inflammatory atrophy could be a connection between prostatitis and prostatic carcinoma in a progressive process from proliferative inflammatory atrophy to prostatic intraepithelial neoplasm,<sup>(23,25,26)</sup> induced by infection and inflammation causing cellular damage by free radicals or genetic alterations.<sup>(27,28)</sup> The findings associating infection with prostatic carcinoma include detection of bacteria in prostatic specimens and experimental studies in mice.<sup>(29-31)</sup> Bacterial DNA sequences of urogenital pathogens and bacterial sequences not reported previously were detected in 19.6% of patients with prostate cancer and 46.4% of those with CPPS.<sup>(30)</sup> On the other hand, in an experimental study on a mouse model of chronic bacterial prostatitis induced by *Escherichia coli*, it was shown that chronic inflammation leads to severe dysplasia and atypical hyperplasia in the prostate.<sup>(31)</sup>

### Benign Prostatic Hyperplasia

Prostatitis and BPH are the most common benign diseases of the prostate gland.<sup>(32)</sup> It is also well recognized by both urologists and pathologists that BPH and prostatitis can coexist.<sup>(33)</sup> The *National Institute of Health's* classification of prostatitis includes the following categories: category I is acute bacterial prostatitis; category

II, symptomatic chronic bacterial prostatitis; category III, chronic pelvic pain syndrome (chronic nonbacterial prostatitis/prostatodynia); and category IV, asymptomatic prostatitis (bacterial or nonbacterial). The association between prostatic inflammation and BPH and the bacterial presence in association with BPH has been documented.<sup>(35)</sup> The clinical significance of asymptomatic Category IV chronic prostatitis associated with BPH has yet to be determined.<sup>(36)</sup>

### Interstitial cystitis

To date, most of the studies have not supported any role for *H pylori* in the pathogenesis of interstitial cystitis.<sup>(37,38)</sup>

### Bladder Cancer

There are some reports of MALT lymphoma arising in the bladder.<sup>(39,40)</sup> Since a history of chronic cystitis is common among patients with MALT lymphoma of the bladder,<sup>(41)</sup> a relation between chronic antigenic stimulation with infectious agents and the occurrence of this malignancy has been postulated. A large body of data have implicated *H pylori* in the pathogenesis of bladder MALT lymphoma, and regression of MALT lymphoma by eradication of *H pylori* has been reported.<sup>(42)</sup> Since the success of eradication by antibiotic therapy is hampered by the occurrence of antibiotic-resistant strains, it has been hypothesized that intravesical vacA-based vaccines against *H pylori* may protect against the development of bladder MALT lymphoma in patients with chronic cystitis, who are at high risk of developing this tumor.<sup>(43)</sup> On the other hand, in an animal study, researchers transurethrally inoculated *H pylori* into the mouse urinary tract and observed that the organism established infection and induced inflammation in the urinary bladder and the pelvis.<sup>(44)</sup>

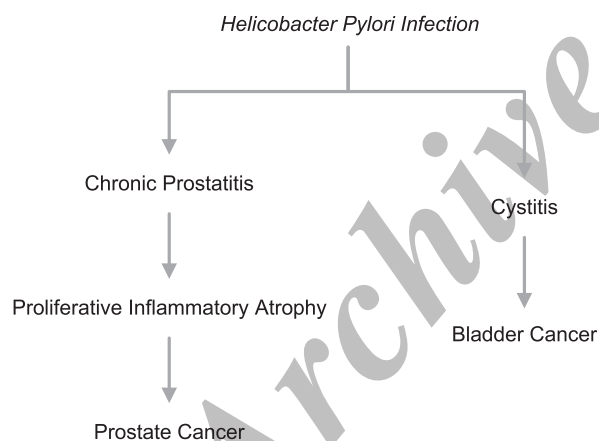
### Kidney Diseases

The prevalence of *H Pylori* infection in kidney transplant recipients is quite variable. Some authors have found it to be quite low (38%),<sup>(45)</sup> while others have reported its incidence rate up to 80%.<sup>(46)</sup> In uremic patients who are known to be infected with *H pylori*, it has been recommended

to eradicate *H pylori* infection prior to kidney transplantation to avoid a long-term significant increase of gastric and/or duodenal peptic ulcer disease.<sup>(47)</sup> A primary MALT lymphoma of the kidney was reported in a 50-year-old man who was infected with *H pylori*.<sup>(48)</sup>

## CONCLUSION

Based on the above summary of the literature, a model relating *H pylori* infection to prostate and bladder diseases can be hypothesized (Figure). However this proposed model has many gaps to be proved and investigated. This model has been proposed to stimulate the collaborative work between the urologists and other scientists to explore this field which is underinvestigated and full of knowledge gaps. If *H pylori* is found to have a significant role in urological diseases, prevention of bladder and prostate cancers by eradication of *H pylori* infection may become a reality like what happened in the treatment of peptic ulcer disease and gastric cancer.



Hypothetical model for the relation of *Helicobacter pylori* infection to urological diseases.

## CONFLICT OF INTEREST

None declared.

## REFERENCES

- Forman D, Newell DG, Fullerton F, et al. Association between infection with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation. *BMJ*. 1991;302:1302-5.
- Bayerdorffer E, Neubauer A, Rudolph B, et al. Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue type after cure of *Helicobacter pylori* infection. *MALT Lymphoma Study Group*. *Lancet*. 1995;345:1591-4.
- Tytgat GN. Review article: treatments that impact favourably upon the eradication of *Helicobacter pylori* and ulcer recurrence. *Aliment Pharmacol Ther*. 1994;8:359-68.
- Correa P. The epidemiology and pathogenesis of chronic gastritis: three etiologic entities. *Front Gastrointest Res*. 1980;6:98-108.
- Patel P, Mendall MA, Carrington D, et al. Association of *Helicobacter pylori* and *Chlamydia pneumoniae* infections with coronary heart disease and cardiovascular risk factors. *BMJ*. 1995;311:711-4.
- Kanbay M, Kanbay A, Boyacioglu S. *Helicobacter pylori* infection as a possible risk factor for respiratory system disease: a review of the literature. *Respir Med*. 2007;101:203-9.
- Pellicano R, Mazzaferro V, Grigioni WF, et al. *Helicobacter* species sequences in liver samples from patients with and without hepatocellular carcinoma. *World J Gastroenterol*. 2004;10:598-601.
- Rebora A, Drago F, Picciotto A. *Helicobacter pylori* in patients with rosacea. *Am J Gastroenterol*. 1994;89:1603-4.
- Nagashima R, Maeda K, Yuda F, Kudo K, Saitoh M, Takahashi T. *Helicobacter pylori* antigen in the glomeruli of patients with membranous nephropathy. *Virchows Arch*. 1997;431:235-9.
- [No author listed]. Schistosomes, liver flukes and *Helicobacter pylori*. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994. IARC Monogr Eval Carcinog Risks Hum. 1994;61:1-241.
- Correa P. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res*. 1992;52:6735-40.
- Al-Marhoon MS, Nunn S, Soames RW. The association between cagA+ *H. pylori* infection and distal gastric cancer: a proposed model. *Dig Dis Sci*. 2004;49:1116-22.
- Atherton JC. The clinical relevance of strain types of *Helicobacter pylori*. *Gut*. 1997;40:701-3.
- El-Omar EM. The importance of interleukin 1beta in *Helicobacter pylori* associated disease. *Gut*. 2001;48:743-7.
- Crabtree JE. Role of cytokines in pathogenesis of *Helicobacter pylori*-induced mucosal damage. *Dig Dis Sci*. 1998;43:46S-55S.
- Schneider H, Wilbrandt K, Ludwig M, Beutel M, Weidner W. Prostate-related pain in patients with chronic prostatitis/chronic pelvic pain syndrome. *BJU Int*. 2005;95:238-43.
- Khadra A, Fletcher P, Luzzi G, Shattock R, Hay P. Interleukin-8 levels in seminal plasma in chronic prostatitis/chronic pelvic pain syndrome and nonspecific urethritis. *BJU Int*. 2006;97:1043-6.
- Li LJ, Shen ZJ, Lu YL, Fu SZ. The value of endotoxin concentrations in expressed prostatic secretions for the diagnosis and classification of chronic prostatitis.

- BJU Int. 2001;88:536-9.
19. Hochreiter WW, Duncan JL, Schaeffer AJ. Evaluation of the bacterial flora of the prostate using a 16S rRNA gene based polymerase chain reaction. *J Urol.* 2000;163:127-30.
  20. Krieger JN, Riley DE, Roberts MC, Berger RE. Prokaryotic DNA sequences in patients with chronic idiopathic prostatitis. *J Clin Microbiol.* 1996;34:3120-8.
  21. McGregor DH, Cherian R, Weston AP, Lawson L, McAnaw MP. Adenocarcinoid of ileum and appendix, incidentally discovered during exploratory laparotomy for gastric MALT lymphoma, with subsequent diffuse prostatic metastases: report of a case with light, immunohistochemical, and electron microscopic studies. *Dig Dis Sci.* 1999;44:87-95.
  22. Sakr WA, Grignon DJ, Crissman JD, et al. High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20-69: an autopsy study of 249 cases. *In Vivo.* 1994;8:439-43.
  23. Dennis LK, Lynch CF, Torner JC. Epidemiologic association between prostatitis and prostate cancer. *Urology.* 2002;60:78-83.
  24. Roberts RO, Bergstralh EJ, Bass SE, Lieber MM, Jacobsen SJ. Prostatitis as a risk factor for prostate cancer. *Epidemiology.* 2004;15:93-9.
  25. De Marzo AM, Marchi VL, Epstein JI, Nelson WG. Proliferative inflammatory atrophy of the prostate: implications for prostatic carcinogenesis. *Am J Pathol.* 1999;155:1985-92.
  26. Shah R, Mucci NR, Amin A, Macoska JA, Rubin MA. Postatrophic hyperplasia of the prostate gland: neoplastic precursor or innocent bystander? *Am J Pathol.* 2001;158:1767-73.
  27. Bostwick DG, Alexander EE, Singh R, et al. Antioxidant enzyme expression and reactive oxygen species damage in prostatic intraepithelial neoplasia and cancer. *Cancer.* 2000;89:123-34.
  28. Zheng SL, Augustsson-Balter K, Chang B, et al. Sequence variants of toll-like receptor 4 are associated with prostate cancer risk: results from the CAncer Prostate in Sweden Study. *Cancer Res.* 2004;64:2918-22.
  29. Wagenlehner FM, Elkahwaji JE, Algaba F, et al. The role of inflammation and infection in the pathogenesis of prostate carcinoma. *BJU Int.* 2007;100:733-7.
  30. Krieger JN, Riley DE, Vesella RL, Miner DC, Ross SO, Lange PH. Bacterial dna sequences in prostate tissue from patients with prostate cancer and chronic prostatitis. *J Urol.* 2000;164:1221-8.
  31. Elkahwaji JE, Zhong W, Hopkins WJ, Bushman W. Chronic bacterial infection and inflammation incite reactive hyperplasia in a mouse model of chronic prostatitis. *Prostate.* 2007;67:14-21.
  32. Collins MM, Stafford RS, O'Leary MP, Barry MJ. How common is prostatitis? A national survey of physician visits. *J Urol.* 1998;159:1224-8.
  33. Nickel JC. Prostatic inflammation in benign prostatic hyperplasia - the third component? *Can J Urol.* 1994;1:1-4.
  34. National Institutes of Health. Summary Statement: National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Disease workshop on chronic prostatitis. Bethesda: National Institutes of Health; 1995.
  35. Gorelick JI, Senterfit LB, Vaughan ED, Jr. Quantitative bacterial tissue cultures from 209 prostatectomy specimens: findings and implications. *J Urol.* 1988;139:57-60.
  36. Nickel JC, Downey J, Young I, Boag S. Asymptomatic inflammation and/or infection in benign prostatic hyperplasia. *BJU Int.* 1999;84:976-81.
  37. Haq A, Mattocks S, Wong L, et al. Incidence of *Helicobacter pylori* in patients with interstitial cystitis. *Eur Urol.* 2001;40:652-4.
  38. Agarwal M, Dixon RA. A study to detect *Helicobacter pylori* in fresh and archival specimens from patients with interstitial cystitis, using amplification methods. *BJU Int.* 2003;91:814-6.
  39. Kempton CL, Kurtin PJ, Inwards DJ, Wollan P, Bostwick DG. Malignant lymphoma of the bladder: evidence from 36 cases that low-grade lymphoma of the MALT-type is the most common primary bladder lymphoma. *Am J Surg Pathol.* 1997;21:1324-33.
  40. Bates AW, Norton AJ, Baithun SI. Malignant lymphoma of the urinary bladder: a clinicopathological study of 11 cases. *J Clin Pathol.* 2000;53:458-61.
  41. Al-Maghrabi J, Kamel-Reid S, Jewett M, Gospodarowicz M, Wells W, Banerjee D. Primary low-grade B-cell lymphoma of mucosa-associated lymphoid tissue type arising in the urinary bladder: report of 4 cases with molecular genetic analysis. *Arch Pathol Lab Med.* 2001;125:332-6.
  42. van den Bosch J, Kropman RF, Blok P, Wijermans PW. Disappearance of a mucosa-associated lymphoid tissue (MALT) lymphoma of the urinary bladder after treatment for *Helicobacter pylori*. *Eur J Haematol.* 2002;68:187-8.
  43. Pastuszka A, Slusarczyk K, Koszowski T, Kudela G, Kawalski H. Intravesical vaccination against *Helicobacter pylori* in patients with chronic cystitis may confer protection against MALT-type lymphoma of the bladder. *Med Hypotheses.* 2007;69:1160-1.
  44. Isogai H, Isogai E, Kimura K, Fujii N, Yokota K, Oguma K. *Helicobacter pylori* induces inflammation in mouse urinary bladder and pelvis. *Microbiol Immunol.* 1994;38:331-6.
  45. Yildiz A, Besisik F, Akkaya V, et al. *Helicobacter pylori* antibodies in hemodialysis patients and renal transplant recipients. *Clin Transplant.* 1999;13:13-6.
  46. Hruby Z, Myszk-Bijak K, Gosciniak G, et al. *Helicobacter pylori* in kidney allograft recipients: high prevalence of colonization and low incidence of active inflammatory lesions. *Nephron.* 1997;75:25-9.
  47. Cocchiara G, Romano M, Buscemi G, Maione C, Maniaci S, Romano G. Advantage of eradication therapy for *Helicobacter pylori* before kidney transplantation in uremic patients. *Transplant Proc.* 2007;39:3041-3.
  48. Colovic M, Hadzi-Djokic J, Cemerikic V, Colovic R, Jankovic G, Dacic M. Primary MALT lymphoma of the kidney. *Hematol Cell Ther.* 1999;41:229-32.