



Pathogenic Mechanisms of Acute Obstructive Pyelonephritis

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Abstract

Among urological diseases, the most relevant is infection of the urinary tract. Pyelonephritis is on the 5th place in kidney diseases, and obstructive pyelonephritis occurs in 84% of all pyelonephritis. In the world, among the adult population, 100 people per 100,000 of the population suffer from pyelonephritis. In addition, from year to year, there is an increase in purulent forms of acute pyelonephritis by 4–5 times. This pathology is a separated manifestation of such an important urological problem as complicated urinary tract infection, which accounts for 84–86% of all infections. In acute obstructive pyelonephritis, more severe complications such as bacteriotoxic shock and urosepsis may develop. The mortality rate from these dangerous complications reaches 70–90%. In addition, the number of patients with urosepsis and bacteriotoxic shock has increased 4–6 times in recent years. The review presents current literature data on acute obstructive pyelonephritis. The main causes and pathogenetic mechanisms of the disease development are presented.

Edited by: Eli Djulejic

Citation: Sharapatov Y, Turgunov Y, Lavrinenko A. Pathogenic Mechanisms of Acute Obstructive Pyelonephritis. Open Access Maced J Med Sci. 2021 Apr 11; 9(F):124-128.
<https://doi.org/10.3889/oamjms.2021.5876>

Keywords: Obstructive pyelonephritis; Etiology; Pathogenesis

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Received: 10-Feb-2021

Revised: 26-Mar-2021

Accepted: 01-Apr-2021

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Funding: This research did not receive any financial support.

Competing Interest: The authors have declared that no competing interest exists.

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Introduction

Pyelonephritis is a non-specific inflammatory process of the tissues of the kidneys and renal pelvis with a predominant lesion of the tubulointerstitium, which is the most common infectious disease of the urinary tract among all age groups [1].

Acute pyelonephritis is inflammation of renal parenchyma caused by microorganisms, which can be dangerous for organs and human's life and lead to kidney scarring. In general, in these cases, bacteria rise from the lower sections of urinary tracts, also it can reach the kidneys through the blood. Acute obstructive pyelonephritis is type of pyelonephritis, caused by obstruction of the upper urinary tracts by urinary stones or stricture of the ureters and other external factors [2].

Obstructive pyelonephritis is one of the most actual problems of modern urology, which found in the urologist's practice. Bacteriotoxic shock and urosepsis can be generated by acute purulent pyelonephritis. In this case, the mortality rate is 70–90% [2], [3].

Epidemiology

Pyelonephritis takes 5th place of kidney diseases and obstructive pyelonephritis occurs in 84% of all types of pyelonephritis. In the world among adults, 100 out of 100,000 people get suffer from pyelonephritis [4]. Moreover, the number of patients with urosepsis and bacteriotoxic shock in recent years has increased 4–6 times. Besides, year after year, there is an increase in purulent forms of acute pyelonephritis by 4–5 times. This ailment is the separate manifestation of such important urological problem as complicated infection of urinary tracts, which accounts 84% of all types of infections. According to authors, obstructive pyelonephritis occurs in 89.3% of patients with different urological diseases and complicates them [3], [4]. Calculous pyelonephritis occurs in 95–98% of patients [5].

Among women, aged 20–50, infection of urinary tracts occurs 50 times more often than in men group. It is because of anatomical and physiological features and changes of hormone's levels. Pregnant women often suffer from pyelonephritis. Acute pyelonephritis takes second place among extragenital diseases, which complicates pregnancy [4], [6].

Etiology

Obstructive pyelonephritis arise from several pathological factors, such as contamination of urinary tracts by pathological flora, congestion of urine caused by obstructive factors, impact of subatrophic and sclerotic changes of urinary tracts as a result of immunodeficiency, which lead to decrease of the ability of the epithelium to resist infection, the existence of inflammatory diseases, and hypoandrogenic-hypoestrogenic condition of elderly people. Thus, obstructive pyelonephritis can complicate all types of urological case or anomaly of kidney and urinary tracts development [3], [7].

The main causes of infectious complications are systemic inflammatory processes, hypoandrogenic-hypoestrogenic condition of elderly people, resurgery of bladder, violation of the antiseptic rules during endoscopic examination and catheterization, and prolonged staying of nephrostomy drains and stents [7], [8], [9].

Risk of infection is very high during all urological infections. It is because of mucosal damage of urinary tracts during operation and contact with infected urine. Frequently infectious complications develop after such surgeries as transurethral resection of prostate, resection of bladder, transvesical prostatectomy, radical prostatectomy, nephrolithotomy, nephrectomy, and plastic of ureter using colon [1].

There is an increase in the number of resistant strains of pathogenic bacteria to most of the antibiotics recent years, also rises among of patients with decreased immunological reactivity. This promotes growth of acute forms, which proceeds into purulently destructive types of diseases of the urinary tract's organs [10].

There are 95% of cases of polymicrobial bacteriuria among patients with prolonged catheterization of the urinary tract. It is connected with emergence of bladder's catheter, drainage tubes, biological membranes, and incrustation of their surfaces by phosphates and struvites. The emergence of specific resistance to antibiotic of persistent bacteria within the biological membranes can be limited by preventive antibiotic therapy [11], [12], [13], [14].

Obstructive pyelonephritis manifests by a combination of local and general symptoms. During remission general symptoms decrease, but symptoms of basic urological ailment persist (urolithiasis disease, prostatitis, benign prostatic hyperplasia, upper urinary tract obstruction, and hydronephrosis) [3].

According to the authors, there are two groups of urinary tracts obstruction's reasons that lead to mechanical or dynamic urinary disorders: Mechanical obstruction caused by urinary stones, cicatricial bladder stenosis, compression of the ureter, ureterocele, tumor, and external and internal ectopia of the ureteral orifices. Herewith, infravesical obstruction is one of the factors, which affects

to the occurrence of pyelonephritis. Neurogenic bladder dysfunction after stroke takes important place in the development of pyelonephritis in elderly group of people. Damage of parenchymal cells, lesion of lipid metabolism, and large accumulation of calcium in cells with its lesion of transmembrane transportation affect on the development of infection with urolithiasis. Dynamic obstruction is generated by such reasons as dysfunction of the bladder's muscular tissue (neurosystemic dysplasia), urinary reflux caused by pathology of the prostate, doubling of the ureters, and ureterocele. These factors are favorable basis for persistence and recurrence of infection and they lead to acute purulent kidney damage [15], [16].

Along with duration of obstruction, level of localization takes place in the development of complications. According to research, the risk of infection's generalization is higher with proximal obstruction of upper urinary tracts comparing to distal obstruction. Therefore, the location of obstruction's factor has a significant effect on the development of the inflammatory process in the kidneys. Consequently, conditions such as a high risk of pyelorenal, pyelovenous, and pyelolymphatic reflux can develop, which can trigger systemic inflammatory processes and sepsis [16].

Gram-negative bacteria play the main role in occurrence of obstructive pyelonephritis. According to the authors, in 50% of cases, the most common infectious agent is *Escherichia coli* and other: *Proteus mirabilis*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Citrobacter* spp., and *Pseudomonas aeruginosa*. In 10–15% of cases, infectious agents are Gram-negative bacteria: *Staphylococcus aureus*, *Streptococcus faecalis*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Staphylococcus saprophyticus*, and *Staphylococcus epidermidis* [7], [11].

According to research, in patients with complicated bladder infection in 57.5% of cases, *E. coli* in was detected in laboratory tests of urine. Among other infections agents are *K. pneumoniae*, *Enterococcus* spp., *P. mirabilis*, *P. aeruginosa*, *Citrobacter* spp., *S. aureus*, *E. cloacae*, *S. saprophyticus*, *Klebsiella* spp., *Enterobacter aerogenes*, and *Streptococcus agalactiae* [17], [18], [19], [20].

According to an investigation of the European Association of Urology, in urine tests of people, who suffered from pyelonephritis were often found such infections as *E. coli*, *Proteus*, *Klebsiella*, *Pseudomonas* and *Serratia* spp. Wherein, *Enterobacteriaceae* and *E. coli* were found in 60–75% of cases [20].

Pathogenesis

Urinary tract infection is the main factor of pathogenesis of pyelonephritis. Ascending way of

infection facilitates adhesion of uropathogenic bacteria. These bacteria have specific adaptation, called fimbria. Due to fimbria, bacteria can adhere to the mucous layers of the urinary organs and move to the upper part of urinary tracts [21], [22].

The adhesion of pathogenic bacterial strains to the cell's membrane leads to the production of inflammatory cytokines. The activation of cytokine synthesis leads to the transition of phagocytes to subepithelial tissues. This is the beginning of apoptosis. As result, pathogenic bacteria penetrate into the deep layers of the epithelium. In this layer, cells do not have a protective ability [21], [22], [23], [24].

These patterns were identified when urinary tract infections were caused by pathogenic strains of *E. coli*: Gram-negative pathogens contain capsular O-antigens and K-antigens, as well as p-fimbria, which is associated with pyelonephritis. K-antigens protect bacteria from opsonization and phagocytosis. O-antigens are endotoxic. As result, O-antigen damages innervation of ureter, thus urosthesis occurs. Bacteria with P-fimbriae in the surface layers have a high adhesion capacity, which protects the bacterium from phagocytosis. Fimbria in bacteria and adhesin proteins associated with them causes adhesion to the surface cells of the epithelium of the mucous membrane of the urinary organs. In the absence of fimbria, adhesion becomes very weak. Adhesion is facilitated due to the hydrophobicity of the surface part of the mucous membrane, carbohydrate polymer in bacteria, polysaccharides, polymers, and high molecular weight [24], [25].

At the edge of the P-fimbria, which contains the pathogen *E. coli*, there are adhesion molecules, which are a receptor on the surface of the urothelium. This leads to the emergence and colonization of urinary infection. The endotoxins and exotoxins of *E. coli* are pathogenic factors, more precise, lipopolysaccharides (O-antigen) of the cell layer, cytotoxic necrotic factor (only uropathogenic strains are found), alpha-hemolysin, and P-fimbrial necrotic factor. The severity of urinary tract infection is regulated by the activity of these factors [25], [26], [27].

When bacteria adhere to the surface of the urothelium, their metabolism is transformed, the fibers contract, and this is a signal for the expression of genes of *E. coli* virulence. *E. coli* rises up the urinary tract, primarily into the mucous membrane, and then into the muscle layer. Urinary ability is impaired, the internal space expands. That's way pyelovenous reflux occurs because of an increase in pressure and compression of the parenchyma bacteria penetrate into the parenchyma and pyelonephritis occurs [28], [29].

Recently, scientific sources often ask about the role of bacterial translocation in the pathogenesis of pyelonephritis [30], [31]. Bacterial translocation is accompanied by the same intensity in all parts of the intestine, but more in the small intestine than in the large intestine. Experimental studies stated that the occurrence

of acute pyelonephritis is due to the translocation of bacteria from the small intestine [30], [34]

In studies carried out in 70% of patients with acute pyelonephritis, which arose in conditions of primary dysbiosis, the cause of the development of an acute purulent process in the kidneys was the translocation of pathogenic microflora from the intestine to the kidneys [31], [32].

In most cases, when urodynamics is impaired, the development of acute pyelonephritis is promoted by the most common representative of the intestinal biocenosis, *E. coli* [33], [34]. As a person's age increases, a decrease in the intestinal barrier function is observed, which leads to a more pronounced translocation of bacteria in the kidneys, and, accordingly, increases the risk of an inflammatory process [35], [36].

When pyelonephritis occurs, the degree of intestinal translocation to the kidney, a direct dependence on the level of colony-forming units and the duration of obstructions, has been established. Microorganisms, after overcoming human immunological barriers, appear in the lymph blood channel, hematological dissemination occurs, which ends with an infectious lesion of the renal tissue [35], [37].

Bacterial translocation from the intestine can also be at a low level in healthy people, and its consequences in the form of the development of renal infection are observed only with the intensity of this process and the introduction of uropathogenic organisms into it. As a result of experiments on animals, the highest concentration of intestinal bacteria was observed in the mesenteric lymph nodes, liver, spleen, lungs, and soft tissues [28], [35].

As a result of a clinical study, an increase in intra-abdominal pressure in acute surgical diseases increases the concentration of a biomarker sCD14. In the study groups where there is an increase in intra-abdominal pressure (higher than 25 mmHg), there is a sharp jump in the concentration of sCD14, which indicates the beginning of enterogenic translocation of bacterial flora into the bloodstream and the development of a "preseptic" state [38].

For the experiments during the study, which was aimed on detailing the bacterial translocation, an experimental model of obstructive intestinal obstruction was created in laboratory animals, followed by the study of the translocation pathways of green fluorescent protein (GFP)-producing strains of *E. coli*. In animals with an identified translocation of this strain, the number of colony-forming units ranged from 10^4 to 10^8 per ml, depending on the organ. The highest contamination was observed in homogenates of the kidneys and lungs (10^8 per ml) and the lowest in homogenates of the mesentery and spleen. The properties of GFP penetration through the cell membrane make it an optimal marker for the diagnosis of cases associated with translocation of microflora [30], [32], [39].

Conclusion

This state of affairs regarding the translocation of bacteria makes it possible to express doubts regarding the upward penetration of microorganisms into the kidney tissue. A certain number of patients with urinary tract infections do not have objective signs of impaired urine formation and urine passage through the urinary organs. Setting up an experiment aimed at identifying the role of intestinal flora translocation in the formation of urinary tract infection will put an end to this issue.

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