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Infected Urinary Stones, Endotoxins and Urosepsis

Joel Gustavo Gómez-Núñez[1], Ulises M. Alvarez[2], Francisco Fernández[3], Jorge Gutiérrez-Aceves[1], Luz María López-Marín[3] and Achim M. Loske[3]
[1]*Nuevo Hospital Civil de Guadalajara, Universidad de Guadalajara, Guadalajara Jal. and Instituto de Endourología, Hospital Puerta de Hierro, Zapopan Jal.,*
[2]*Posgrado en Ciencias Químicas, Facultad de Química, Universidad Nacional Autónoma de México*
[3]*Centro de Física Aplicada y Tecnología Avanzada, Universidad Nacional Autónoma de México, México*

1. Introduction

Urinary tract infections (UTIs) and their complications represent one of the most common causes of medical consultation with high cost to medical services and high morbidity and mortality. Urinary stones are another medical challenge that represents an acute or chronic clinical setting for patients requiring most of the time active treatment, either as an invasive or as a non-invasive management, thus increasing costs and risks. The combination of both clinical scenarios —urinary tract infection and urinary stone— is common and can trigger a systemic inflammatory response syndrome (SIRS) before, during or after medical treatment (i.e. antibiotics) and/or surgical manipulation of infected urinary stones. It is believed that SIRS is due to the release of endotoxins from infected urinary stones, developing endotoxemia, bacteremia and urosepsis. If not controlled, multiple organ failure syndrome (MOF) and death of the patient may occur. Urologists are familiar with these scenarios where not only prevention and diagnosis but also an early and appropriated treatment is crucial. Unfortunately, the use of prophylactic antibiotics does not guarantee prevention of these fatalities. The aim of this chapter is to review the evidence of possible endotoxin release during invasive and non-invasive treatment of infected urinary stones as a trigger of SIRS and sepsis.

2. Urinary tract infections

Urinary tract infections are the second most frequent infections in developed countries and uropathogenic *Escherichia coli* (*E. coli*) a non-urea-splitting bacterium represents 80 % of uncomplicated UTIs (Oelschlaeger et al., 2002). There is a geographic variation about *E. coli* and several other Gram-negative, as well as Gram-positive bacteria and fungi causing complicated and uncomplicated UTIs among specific populations. Virulence of bacteria causing UTIs is determinant for progression of the disease. Some virulence factors in

uropathogenic *E. Coli*, as adhesins (Type 1 pili, Dr-family pili, P fimbriae, F1C fimbriae, S fimbriae) and toxins (CNF1, Hemolysin and Sat) (Oelschlaeger et al., 2002), could explain the systemic forms of invasion of the bloodstream by some *Enterobacteriaceae* in possible synergism with the release of endotoxins that may result in SIRS and urosepsis. These virulence factors are reviewed elsewhere in this book.

2.1 Urinary bacterial epidemiology

Urinary tract infections in Western countries are mainly caused by *E. coli* (90 %), *Proteus* spp, *Klebsiella* spp, and *Pseudomonas* spp (McRae & Shortliffe, 2000; Bochud & Calandra, 2003). Variation in proportions and specific populations have been reported and described (Foxman, 2003; Savas et al., 2006). Bacterial resistance is another important issue that increases morbidity and mortality. For further details and specific information about bacterial epidemiology in UTIs we invite the reader to consult other sections of this book.

2.1.1 Endotoxins

To invade hosts, bacteria use a variety of substances, some of them are essential for their survival. In Gram-negative bacteria, specific molecular patterns composed of lipid and sugar moieties represent some of the most toxic virulence factors of bacterial origin. Structurally classified as lipopolysaccharides (LPS), these substances have no chemical homologs among human cells, and are known as endotoxins, to denote their ability for causing fever, shock and organ injury when released in mammalian endothelial vessels (Beutler, 2000). The presence of endotoxins in the blood-stream is named endotoxemia and can trigger SIRS. LPS have specific structural motifs which are typical of different bacterial species. However, all of them are known to induce endotoxemia and sepsis (Bochud & Calandra, 2003). Endotoxins are known to be recognized by cell-surface proteins, the LPS receptors, which are widely distributed in animals as part of their immune systems (from insects to vertebrates). However, a strong inflammatory reaction after LPS recognition is restricted to a handful of species, including humans (Beutler, 2000). According to numerous studies in cellular and animal models, recognition of LPS by their receptors initiate a cascade of intracellular signals guiding the secretion of pro-inflammatory mediators (Beutler, 2000; Triantafilou & Triantafilou, 2005). An emerging concern is the toxicity of LPS after microbial death, especially in the context of hospital-acquired infections. In fact, released LPS keep their full toxic potential, unless inactivation processes take place in the host to degrade endotoxins (Munford et al., 2009).

3. Urinary stones

Urinary stones have been reported in human history since antiquity. Traditionally, stones have been classified according to their main mineral content. The etiology of urinary stones is wide, including chronic dehydration, urinary tract malformations, obstructed uropathy, metabolic diseases (i.e. hyperparathyroidism, gout, and obesity), foreign body inside urinary tract, infections, etc. The risk for stone disease in patients of developed countries is close to 10 % life-long. An increase in the incidence of stone disease related with changes in the life style, modifications on the diet, morbid obesity surgery syndrome and new drugs has been reported in Western countries in recent years. For example, in the United States, an increase of 37 % in stone disease was observed over the last 20 years (Straub & Hautmann,

2005). A variation in the frequency and in the composition of the minerals forming the urinary stones was also observed.

There is a large variety of urinary stone compositions. If the main component is more than 80 % of the total mass, the stone is named "pure". If the main component is at least 50 % of the stone, it is named mixed. In Western countries, struvite stones used to represent 15-30 % of cases. Nowadays only 2 % of stones are struvite (McALeer et al., 2003; Kramer et al., 2000). The explanation of that decrease is unknown. In developing countries and Eastern countries there is a large variation among incidence, prevalence and stone composition. For example, in India a report including 1050 urinary calculi from surgically treated patients (900 renal and 150 ureteral) revealed 93.04 % oxalate calcium stones (80 % calcium oxalate monohydrate [COM] and 20 % calcium oxalate dihydrate [COD]), 1.92 % struvite stones, 1.48 % apatite stones, 0.95 % uric acid stones and 2.96 % mixed stones. Surprisingly, 89.98 % of the staghorn stones consisted of oxalates and only 4.2 % were struvite (Ansari et al., 2005). A study in Japan showed that the most common stone composition was struvite (32.1 %) and mixed calcium oxalate phosphate (22.2 %) (Akagashi et al., 2004). These differences could be explained by variations in ethnics, epigenetics, geographical area, diet, life-style, and different metabolism.

3.1 Infected stones

It has been suggested that urinary stones can be infected mainly in two ways. Stones develop due to several mechanisms which may or may not be associated to obstructive uropathy (i.e. hyperparathyroidism). The first way in which a stone can be infected is by ascending bacteria. Once the stone is formed, ascending bacteria may reach its surface, invade the interstice and become part of it (Takeuchi et al., 1984; Abrahams & Stoller, 2003). Adherence of new minerals could cover and paste bacteria layers. In this case, the stone acts as a reservoir for bacteria. Due to the poor penetration of drugs into the stone matrix the action of antibiotics is limited (Prabakharan et al., 1999). This phenomenon can be the reason of bacterial resistance, repeated, chronic or complicated UTIs in several patients, therefore increasing the risk of urosepsis. The most possible scenario according to the most frequent stone component and urinary bacteria in our Western world is a calcium stone infected with *E. coli*. In this case, the urinary stone forms first and gets infected by bacteria afterwards.

The second scenario is that bacteria living inside the urinary tract and causing chronic UTIs produce the stones. These bacteria are named urea-splitting bacteria. Members of this group are *Proteus*, *Klebsiella*, *Pseudomonas, Providencia, Serratia* spp, *Staphylococcus aureus* and *Ureaplasma urealyticum*, among others. *P. mirabilis* accounts for more than half of all urease-positive urinary infections (Kramer et al., 2000). Urea-splitting bacteria change the urine pH (> 7.2) and allow easier precipitation of phosphate with several compounds, mainly ammonium and magnesium (Abrahams & Stoller, 2003). The result is a compound phosphate named struvite (magnesium-ammonium-phosphate [MAP] stones and/or triple phosphate stones). Another type of phosphate stones are apatite stones (calcium phosphate). The terms "infectious stones" or "infection stones" are used as synonymous of struvite stones and represent up to 15 % of all stones sent for analysis in the Western world (Kramer et al., 2000). Infected stones that contain struvite may originate *de novo*, but often pre-existing stones are infected with urea-splitting bacteria (Kramer et al., 2000). There is evidence that urinary tract infections caused by urease-producing microorganisms are not exclusively related to the formation of struvite stones. Considering this scenario, *Proteus*

mirabilis and struvite stones are the most likely combination. In this case, the risk for urosepsis is also patent.

It has been suggested that some agents named nanobacteria could have a role in the development of calcium-based urinary stones (Kajander & Çiftçioglu, 1998); however, this is not yet well established (Kramer et al., 2000). A prevalence of nanobacteria in 0.5 % of 1000 stones was reported; but nanobacteria are still difficult to identify (Abrahams & Stoller, 2003).

3.1.1 Bacterial epidemiology of infected urinary stones

Urinary stone cultures from fragments retrieved during stone surgery were not a common practice until recently. Negative urine culture before urinary surgery was considered safe. In general urology it has been a routine to have a negative midstream urine culture before doing any endoscopic procedure. Recent studies suggest that voiding urine culture is not representative of upper urinary tract pelvis infection or pelvis infected stone bacteria (Mariappan & Loong, 2004; Mariappan et al., 2005a). A group of 73 patients with unilateral stone-obstructed ureter were treated with ureterorenoscopy and lithotripsy. Midstream urine (MSU) sample culture and sensitivity were performed the morning of the endoscopic surgery. During the procedure a pelvis urine sample and stone fragments were collected for culture and sensitivity with an aseptic technique in a retrograde approach. The authors reported that 25 (34.3 %) patients had positive stone culture, 43 (58.9 %) had positive pelvic urine and 21 (28.8 %) had positive MSU culture. The most common isolated bacterium was *E coli*. The MSU culture and sensitivity test had 30.2 % sensitivity and 73 % specificity to detect pelvic urine culture and sensitivity. The same test had a low positive predictive value and negative predictive value in relation to infected pelvic urine (positive predictive value = 0.62, negative predictive value = 0.42) (Mariappan & Loong, 2004). According to these authors, in case of a ureteral obstructive uropathy secondary to a stone, MSU culture and sensitivity do not represent infected urine proximal to the obstruction or infected stone. Stone components were not analyzed. In conclusion, pelvic urine and stone cultures were considered as a more appropriate indicator of upper urinary tract infection. Collection of the obstructed urine for culture and sensitivity are recommended.

Mariappan and colleagues (2005a) studied a group of 54 patients with renal stones who were candidates for percutaneous nephrolithotomy (PCNL). Various specimens were collected for culture and sensitivity, i.e., MSU sample, bladder urine sample, renal pelvic urine sample and crushed stone sample. The objective of the study was to identify the most predictive analysis of urosepsis. MSU culture was positive in 11.1 % of cases, stone culture was positive in 35.2 % and pelvic urine was positive in 20.4 % of cases. A wide variety of bacteria were isolated. In 37 % of the patients SIRS was developed and 5.5 % experienced septic shock. Pelvic urine culture predicted infected stones better than bladder urine culture. Patients with infected stones or pelvic urine were found to be at a relative risk for urosepsis that was at least four times greater (P = 0.0009). The authors concluded that positive stone and pelvic urine are better predictors of potential urosepsis than bladder urine and recommend routine collections of these specimens. Stone components were not analyzed. The bacterial epidemiology of infected urinary stones also depend on differences in geographic area, strains, bacterial resistance, bacterial virulence, exposure to some kind of antibiotics and environment.

4. Sepsis and urosepsis

Sepsis is an extreme health condition that threatens life of patients with a high cost for the healthcare systems. Reports from US and European surveys have estimated that severe sepsis accounts for 2–11 % of all admissions to hospitals or intensive care units. The most common microbes isolated from patients with severe sepsis and septic shock are Gram negative bacilli (mainly *E. coli*, *Klebsiella* species and *Pseudomonas aeruginosa*) and Gram positive cocci (mainly *Staphylococci* and *Streptpcocci* spp). Most cases of Gram negative sepsis are caused by *E coli* and *Klebsiella* species followed by *P. aeruginosa*. Infections usually occur in the lung, abdomen, bloodstream, or urinary tract (Bochud & Calandra, 2003). In a trial performed in an intensive care unit with 142 septic patients having a urinary catheter, urosepsis occurred in 15.8 % of them (Rosser et al., 1999). Urosepsis in adults comprises approximately 25 % of all sepsis cases and in most cases is due to complicated urinary tract infections (Wagenlehner et al., 2007). An incidence of sepsis associated with obstructed uropathy and urinary stones treated surgically has also been reported in 1.28 % of cases (O'Keeffe et al., 1993). Rao et al. (1991) found an incidence of septic shock after endoscopic manipulation for urinary stone in about 1% of treated patients. Sepsis is an advanced stage of uncontrolled systemic inflammatory response syndrome that may turn toward irreversible multiple organ failure and death.

5. Endotoxins and sepsis

Activation of local and systemic metabolic response to trauma and SIRS is mainly caused by activation of IL-1 and tumor necrosis factor-α (TNF-α). It is well established that after recognition by cognate receptors, LPS trigger the synthesis and release of pro-inflammatory cytokines (Triantafilou & Triantafilou, 2005). Once IL-1 and TNF are secreted, they activate several other reactions like complement factors, exacerbating the host inflammatory response. As a consequence, MOF or death may result. *In vitro* human blood monocytes produce IL-1 and TNF-α when they are exposed to 25 to 50 pg/mL of endotoxin concentration. These endotoxin levels have been reported in the bloodstream of patients during septic shock (Dinarello & Cannon, 1993). In a clinical report of 97 consecutive patients, 56 % developed sepsis syndrome with about 26 pg/mL of TNF-α.; 37 % had 20 pg/mL of IL-1 and in 80 %, 415 pg/mL of IL-6 was detected, including a LPS mean concentration of 2.6 endotoxin units (EU)/mL (1 EU/mL = 0.6 ng/mL) (Casey et al., 1993). The level of procalcitonin has also been used as a sepsis marker. Another assay with healthy volunteers demonstrated elevation of procalcitonin (peak up to about 4 ng/mL at 6 hours) after I.V. administration of 4 ng/kg of body weight of endotoxin derived from *E coli* 0113:H10:k (Dandona et al., 1994). In a new human model of low grade inflammation, 10 healthy male subjects were exposed to 3 ng/kg body weight of endotoxin (LPS) derived from *E. coli* in I.V. bolus injection versus I.V. infusion during 4 hours. Results revealed that TNF-α, IL-6 and neutrophil response were earlier and more pronounced in the bolus trial, suggesting that sudden release of endotoxins triggers faster and higher release of cytokines and inflammatory mediators similar to sepsis. Changes in cytokines measured in the infusion trial would be a more representative model of human systemic low-grade inflammation in chronic disease (Taudorf et al., 2007).

6. Infected urinary stones and urosepsis

In a study on 700 patients, the prevalence of sepsis related with obstructed uropathy and urinary stones treated surgically was 1.28 %. These nine patients developed SIRS and sepsis during 6 hours postoperative. Although males and females were treated in roughly equal proportions, all of the patients who developed severe sepsis were females. There were six deaths accounting for 66 % mortality (O'Keeffe et al., 1993). Septic shock following urinary stone manipulation was reported with an incidence of 1 % and mortality up to 80 % (Rao et al., 1991).

In an effort to predict septicemia following endourological manipulation for stones in the upper urinary tract, 117 patients were studied and classified according to the procedure performed (Rao et al., 1991): Percutaneous nephrolithotomy, push-back/push-bang procedure, double-J and extracorporeal shock wave lithotripsy (SWL), ureteroscopy, SWL alone and only cystoscopy. Blood samples for bacterial culture, endotoxin and tumor necrosis factor assay were collected before, at onset, at the end and one hour after completing the procedure. Preoperative bacteriuria was present in 35 % of the patients. The mean endotoxin level of the entire group —except the cystoscopy group— was 16.2 pg/mL (range 11 to 58.3 pg/mL). In the cystoscopy group the mean endotoxin level was 11.7 pg/mL (range 11 to 12.2 pg/mL). All patients (16) with preoperative endotoxemia had increased levels of endotoxin detected in subsequent samples (mean increase 15 pg/mL, range 0.5 to 64 pg/mL). The tumor necrosis factor was greater than 15 pg/mL in four cases preoperatively. Postoperatively there was elevation of the tumor necrosis factor only in 12 patients. The authors reported that in case of upper urinary tract manipulation, the risk of bacteremia was higher. The risk was greatest after performing the push-back method and least after cystoscopy. Combination of preoperative endotoxemia, bacteriuria and the type of procedure had 85 % of sensitivity, 84 % of specificity and a positive predictive value of 52 % for the development of postoperative bacteremia. A total of 41 patients had pyrexia and 17 patients had rigors and fever 2 to 3 hours after the end of the procedure. No patient suffered septic shock; however, this complication developed in a female patient one week after percutaneous nephrolithotomy. Serum endotoxin and tumor necrosis factor levels after admission of this patient to the intensive care unit were 67.7 pg/mL and 3,827.5 pg/mL, respectively (Rao et al., 1991).

Measurements of LPS were done in 34 renal stones, stored for several months and classified as infection stones (16), i.e., struvite and calcium apatite, and non-infection stones (18) composed of 50 % calcium oxalate monohydrate (McALeer et al., 2003). All stones were weighed, aseptically crushed and aliquots were tested for endotoxins. Four stones of each group were aseptically washed and crushed separately. Washed materials and crushed stones were processed in MacConkey agar culture to recover bacteria colonizing the stones. Mean endotoxin concentration in the infection group was 12,223 ng per gram of stone and 340.3 ng per gram of stone in the non-infection group. The difference was statistically significant ($P = 0.001$). These results reveal an almost 36 times higher concentration of endotoxins in the infection stones. No living bacteria were recovered on the MacConkey plates from crushed stones from neither group. The authors concluded that large amounts of endotoxins can be found in infected renal stones even months after they were removed from the body, and long after viable bacteria could be detected. Furthermore, endotoxin may remain after bacteria are no longer viable or have been killed with antibiotic therapy (Munford et al., 2009). Non-infectious stones can also contain endotoxin but in a lower

amount (McALeer et al., 2003). McALeer et al. (2002) published a case report of an 8 year old boy with a left staghorn calculus treated with holmium laser percutaneous nephrolithotripsy (PCNL). Culture specific antibiotic were administered to the patient, both orally and intravenously, before, during and after surgery. Intraoperative fluid and pleural fluid cultures (urologists lost percutaneous access from lower pole calyx with intraperitoneal extravasation and pleural effusions) were obtained. A urine culture was performed before and after stone manipulation. All samples grew a few colonies of *Proteus mirabilis*. Blood cultures were requested but could not be obtained; serum endotoxin results could not be obtained either. Two hours after procedure the patient developed disseminated intravascular coagulopathy. Twelve hours after stone manipulations the patient died despite aggressive support care. Stone composition was apatite (80%) and struvite (10%). Post-mortem culture of the stone grew several colonies of *Proteus mirabilis.* The assay of the stone fragments for endotoxin showed concentrations of 285,600 pg per gram, suggesting that endotoxemia can induce sepsis syndrome without concomitant bacteremia. The authors concluded that the outstanding endotoxin concentration of the renal stone was the source of the fatal outcome.

There is not a general consensus on how to best prevent sepsis in patients undergoing surgical treatment of urinary stones. Pre-surgical, trans-surgical and post-surgical strategies have been proposed. The combination of multiple factors can prevent, trigger or worsen sepsis. For example, control of metabolic or cardiopulmonary diseases is important. Although antibiotic prophylaxis does not completely avoid the risk of developing sepsis, it is a recommendation for stone surgery according to the American Urological Association (AUA) and the European Association of Urology (EAU) guidelines on urinary tract infection (Grabe et al., 2011; Wolf et al., 2010). It is suggested to define an antibiotic prophylaxis according to local bacterial populations, resistance and antibiotic sensitivity patterns. In a prospective controlled trial, Mariappan et al. (2006) and Bag et al. (2011) reported the beneficial use of one week ciprofloxacin and nitrofurantoin regimen respectively, before percutaneous nephrolithotomy. Furthermore it has been found that renal stones larger than 20 mm are more likely to be culture positive (Mariappan et al., 2005a; 2005b). Mariappan and colleagues (2005a) suggested to obtain pelvic urine and stone samples for culture and sensitivity as a routine during surgical stone procedures, with the aim of administering proper antibiotic regimen if later urosepsis develops. If an unusual urine sample (i.e. turbidity, foully) is obtained, culture and sensitivity is a must. In this case, a nephrostomy tube should be left in place and the initial procedure rescheduled until sterile urine is confirmed.

An increase of pressure inside the urinary tract system generated by the irrigation fluid results in a potential bacterial and endotoxin translocation into the bloodstream. Auge et al. (2004) reported significant reduction in urinary tract pressures using ureteral access sheath if working both in distal ureter and inside the renal pelvis. Bacteria and likely endotoxins may emerge from several kinds of urinary stones and not exclusively from struvite stones (Hugosson et al., 1990; McALeer et al., 2003). In post-surgical stage, the most critical evidences of SIRS are during the first 6 hours post-procedure and seem to correlate with cytokines release into the bloodstream after endotoxin stimulus (Dandona et al., 1994; O'Keeffe et al., 1993; Rao et al., 1991; Taudorf et al., 2007). It has been suggested that if other causes of SIRS different than infection (i.e. cardiogenic or pulmonary events, atelectasis, hypovolemia and pain) have been ruled out and if SIRS persists, then sepsis could be the explanation (Monga, 2005). Close vital signs and symptoms monitoring and high suspicious

index for sepsis is crucial at this stage. Once urosepsis is diagnosed, an early tissue oxygenation, appropriate initial antibiotic therapy, inotropic and nutritional support with invasive monitoring at intensive therapy unit is required. Empirical broad-spectrum antibiotics regimen is prescribed according to local bacteria, sensitivity and resistance patterns. If cultures were performed from bladder urine, pelvis urine or stone sample, direct therapy must be installed as soon as results are obtained (Mariappan et al., 2005b). Wagenlehner and his group (2007) reported that the treatment of urosepsis comprises four major aspects: Early goal-directed therapy, optimal pharmacodynamics exposure to antimicrobials both in blood and in the urinary tract, control of complicating factors in the urinary tract and specific sepsis therapy. They considered that interdisciplinary approach is necessary to achieve an optimal goal of treatment. At any of these stages, it is very important to act as soon as possible if any evidence of initial SIRS and urosepsis is addressed. It is necessary to instruct the patient and relatives once discharged from the hospital, that if SIRS develops, urgent evaluation in an emergency unit is crucial (Rao et al., 1991). There is no doubt that further research is required and that several other issues have to be considered; however, these do not fall within the scope of this chapter.

7. Research on bacterial suspensions and extracorporeal shock wave lithotripsy

Several articles report the bactericidal effect of shock waves *in vitro*; however, results remain controversial. Elbers et al. (1988) observed no effect of shock waves on calculi inoculated with urease-positive calculogenic bacteria. Bacteria from different genera and species have different resistances to physical, chemical and environmental factors; such variations in bacteria may determine the degree of susceptibility to shock waves. For instance, we have previously found that shock wave-induced cavitation contributes to *L. monocytogenes*, *S. typhimurium* and *E. coli* O157:H7 inactivation; however, *L. monocytogenes* was more sensitive to shock waves than *E. coli* O157:H7 (Alvarez et al., 2004). Kerfoot and colleagues (1992) found no effect of shock wave application on *S. aureus*; however von Eiff et al. (2000) reported inactivation of a different strain of the same bacteria. Similarly, whereas Ohshima et al. (1991) observed no effect of shock waves on the viability of *E. coli* strains DSM 1077 and JM 109/pKPDH2, Loske et al. (1999) reported inactivation of *E. coli* strain ATCC 10536. Patel et al. (2005) reported no effect of shock waves on a five-stain cocktail of *E. coli* O157:H7, whereas Podolak et al. (2005) reported shock wave inactivation of a slightly different cocktail of the same *E. coli*. Various shock wave generators were used by these authors, which may explain their different results. When performing *in vitro* exposure of bacteria in suspension by shock waves generated with electrohydraulic shock wave generators, the electromagnetic radiation produced at the spark gap contributes to microorganism inactivation. During SWL this radiation (visible and UV) does not penetrate into the calculus. Besides, electromagnetic radiation, compression, tensile stress, and cavitation may also damage bacteria. Cavitation is produced by the trailing tensile pulse of the shock wave. A cloud of bubbles forms at the focus of every lithotripter after the passage of each shock wave. During collapse, they create secondary shock waves, powerful jet blasts of fluid (microjets), high temperature gradients, and free radicals (Crum, 1988). If a second shock wave is sent during, or shortly after, the stable phase of the bubbles, their collapse can be intensified. This technique, referred to as "tandem SWL" has proven to reduce *in vivo* SWL treatment time by 50 % (Fernández et al., 2009). To test the efficiency of tandem shock

waves to inactivate bacteria, Alvarez and colleagues (2008) used an experimental piezoelectric tandem shock wave generator that generates two shock waves shifted in time. The effects of single and tandem shock waves on the viability of *L. monocytogenes* and *E. coli* O157:H7 suspensions were studied. Tandem shock waves were generated at delays of 450 and 900 microseconds. No effect on bacteria viability was reported after exposure to 8,000 single shock waves, but significant bacteria inactivation was reported after 3,400 tandem shock waves. The delay yielding the highest inactivation was 900 microseconds.

8. Research with stone models

Efforts to develop an ideal stone model have been done worldwide to perform *in vitro* and *in vivo* fragmentation tests exposing artificial stone models to different lithotripter energy settings. To study the inactivation of bacteria by shock waves and the bactericidal effect of different intracorporeal lithotripters, we developed an artificial calcium sulphate stone model infected homogenously with *E. coli*, a mixed struvite-calcium sulphate stone infected with *P. mirabilis* and a calcium sulphate stone infected with *P. mirabilis*.

8.1 The bactericidal effect of intracorporeal lithotripters

Only a few authors report results on the interaction of infected urinary stones with intracorporeal lithotripters. Artificial kidney stones, infected with *E. coli*, were manufactured by our research group to evaluate the bactericidal effect of shock waves, and the differences on intra-bacterial protein release produced by four different intracorporeal lithotripters. The stone models were exposed to a holmium laser, an electrohydraulic, a pneumatic and an ultrasonic intracorporeal lithotripter using two energy settings. Non-infected control stones were manufactured by casting a mixture of gypsum cement, Velmix-stone (Kerr Division of Syborn Corp., Romulus, MI, USA) and distilled water in cylindrical molds (diameter = 10 mm, height = 10 mm). A saline solution containing *E. coli* was used instead of distilled water to manufacture the infected stones. Cells were obtained in the stationary phase of growth. Stones were placed on a copper mesh with 1.8 mm by 1.8 mm openings at the bottom of a specially designed lucite test tube. The lucite tube was placed inside a standard laboratory test tube, containing 10 mL of saline solution. The tip of the lithotripter was introduced inside the lucite tube (see Figure 1). Five infected stones were fragmented with each lithotripter at each energy level (low and high) during a fixed time. After treatment all remaining stone fragments were crushed with a hand press. The suspension containing stone powder and bacteria was centrifuged, serially diluted and incubated on agar plates. Viable counts were made by plating on trypticase soy agar supplemented with 0.6 % (w/v) yeast extract (TSAY). Bactericidal action was defined as the logarithmic difference of colony forming units (CFU) per milliliter between untreated and treated stones. To study the effect of the lithotripters on bacteria living outside the stone, an *E. coli* suspension was exposed to the action of each lithotripter, using the same energy settings and exposure times as for infected stones. The process was repeated five times for each lithotripter at each energy setting. Stone fragmentation of infected stones was repeated as described before, in order to measure the release of protein (LPS) as a result of *in vitro* lithotripsy. After treatment, certain amount of the suspension was centrifuged and placed inside a spectrophotometer to measure absorbance at 280 nm. Results revealed that the variation in the amount of bacteria inside the stones was not significant. Complete inactivation resulted with the electrohydraulic lithotripter at both energy levels. No difference was observed between

inactivation obtained with the other lithotripters at their low energy settings. Increasing the energy resulted in higher bacteria inactivation for the laser, pneumatic and ultrasonic lithotripter. The laser lithotripter produced the lowest bacteria inactivation. Inactivation increased as the energy setting of the laser, pneumatic and ultrasonic lithotripter was changed from low to high. No bacteria inactivation was observed using the pneumatic lithotripter in an *E. coli* suspension alone. No viable bacteria could be observed after using the laser, the electrohydraulic and the ultrasonic lithotripter in the infected suspension (without stone). Maximum protein release occurred at low energy with the electrohydraulic lithotripter and protein was denaturized by this lithotripter at the high energy setting. No difference was observed between the amount of protein released with the laser, the pneumatic, and the ultrasonic lithotripters at both energy levels. The four lithotripters inactivated more than 99 % of the initial amount of bacteria; however, this antibacterial effect does not necessarily indicate that lithotripters sterilize stone fragments. The presence of free endotoxins liberated from bacteria after lithotripsy may increase the risk of sepsis. These findings could explain local and systemic inflammation response by the immune system of some patients developing in SIRS and sepsis (Gutiérrez et al., 2008).

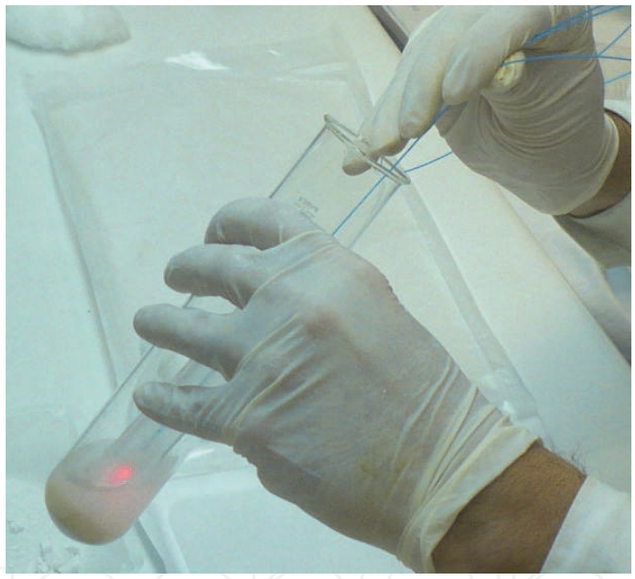

Fig. 1. Photograph of the special lucite test tube with copper mesh bottom (not seen) placed inside a standard glass laboratory test tube during *in vitro* fragmentation of an artificial infected kidney stone with a laser lithotripter.

Our group also studied the effect of the four above-mentioned intracorporeal lithotripters on the bacterial inactivation of artificial struvite stones inoculated with *Proteus mirabilis*. Again two energy settings were tested with each lithotripter, with exception of the pneumatic lithotripter, which was used only at one intensity. Calcium sulphate stones and struvite-gypsum stones were manufactured and homogeneously infected with *P. mirabilis*. Details on the methodology of producing infected stones can be found in the literature (Gutiérrez et al., 2008; Gómez-Núñez et al., 2009). Infected calcium sulphate and infected struvite-gypsum stones were exposed to each device at each intensity level until complete fragmentation. The treatment time was dependant on the lithotripter and the intensity level. After *in vitro* lithotripsy, the suspension containing stone debris and *P. mirabilis* was diluted

and incubated on agar plates. A sham group of non-treated infected stones was crushed with a hand press to determine the amount of bacteria surviving inside the artificial stones. The whole experiment was repeated three times. The initial viable count in the sham group was about 6.02 $\log_{10}$ CFU/mL. Results revealed that all lithotripters inactivated a high percentage of *P. mirabilis*. No statistically significant difference was observed between calcium sulphate and infected struvite-gypsum stones (Gómez-Núñez et al., 2009). Prabakharan and colleagues (1999) reported an *in vitro* assay using 46 "natural" struvite stone models (fragments), sterilized in an autoclave and reinfected with *P. mirabilis*, coming from patients treated for urinary stones. The stones were exposed to shock waves generated with an extracorporeal lithotripter, as well as to the action of an ultrasonic, an electrohydraulic, a pneumatic, and a Holium:YAG laser intracorporeal lithotripter. No bacterial inactivation was observed, except for the laser intracorporeal lithotripter. A possible lack of this trial could be the variability of stone shape, composition, and non-homogeneous bacteria colonization of the stone.

In conclusion, it seems that the stone material plays a minor role regarding bacterial inactivation due to intracorporeal lithotripsy. Furthermore, according to our results, intracorporeal lithotripters are very harmful to bacteria; however, whether bacterial destruction is desirable or not is still unknown.

8.2 The bactericidal effect of extracorporeal lithotripters

A reduction in bacteriuria and resolution of urinary tract infection after SWL has been reported by several authors (Beck & Riehle, 1991; Gerdesmeyer et al., 2005; Michaels et al., 1988; Pode et al., 1988); however, it is not known if the stone protects bacteria or if other mechanisms, such as shear, contribute to the bactericidal effect of shock waves. To answer these questions, infected stones were exposed *in vitro* to shock waves from both an electrohydraulic and a piezoelectric lithotripter. Energy comparable to that used in SWL was used, so that the stress on the bacteria was similar to that experienced by bacteria living inside calculi during shock wave treatment. Two types of artificial kidney stones (soft and hard) were manufactured by mixing different amounts of gypsum cement and Velmix-stone, as explained in the previous section. In this case the length and diameter of the models were about 7 mm and 8 mm, respectively. *Salmonella enterica* serovar *typhimurium* in the stationary phase of growth was used to inoculate the stones. Stones to be treated were placed inside a translucent polypropylene bag, filled with deionized water, heat sealed, and centered at the lithotripter focus. All fragments from shock wave treated stones, as well as a set of intact control stones, were completely crushed using a hand press until stone powder was obtained. All bags were opened and dilutions of the suspension containing stone powder and bacteria were inoculated on TSAY plates and incubated at 35 °C. About 29 % of all bacteria were inactivated with the piezoelectric lithotripter and 14 % with the electrohydraulic lithotripter. This study demonstrated that the bactericidal action of shock waves is weaker inside the stones than in the fluid outside them (Quintero et al., 2008). Whether it is desirable for a lithotripter to inactivate instead of destroying bacteria is still to be answered.

9. Conclusions

Sepsis is a serious health condition with high mortality and cost. Advances in the manufacture of standardized infected stone models and *in vitro* assays could help to better

understand the pathophysiology of sepsis associated to urinary tract infection alone and UTIs with infected stones. *In vitro* fragmentation of artificial stones could also help to understand and prevent the pathophysiology and phases of Gram negative sepsis. According to our initial results, living bacteria infecting urinary stones release endotoxins as part of their metabolic activity or as a consequence of bacteria lysis during intracorporeal and extracorporeal lithotripsy. Bacteria fragments could be a source of endotoxin even in the case of urine voiding and urine pelvis negative cultures. Further research related with release of LPS during lithotripsy and its relation with triggering sepsis is urgently needed. Absorption of LPS into the bloodstream by reflux due to open pyelolymphatic and pyelovenous channels during obstructive uropathy, bacterial translocation, interaction with lithotripters, increased irrigation pressure during endoscopic surgery, and rupture of the hemato-urinary barrier (microtrauma) should be studied. On the other hand, recent investigations (Soriano et al., 2005; Opal, 2003) have been revealing valuable information about sepsis mediators, such as cytokines, including tumor necrosis factor (TNF), interferons, complement factors or nitric oxide, anti-LPS host hydrolases, and bacterial factors. Translational studies focusing clinical strategies based on benchmark discoveries regarding LPS-triggered toxemia therefore represent a major task for the urologist. The main highlights of this chapter are summarized in Table 1.

Highlights
• During sepsis, a 25 - 50 pg/mL LPS concentration has been reported in the bloodstream. • LPS concentrations of up to 285,600 pg per gram stone have been reported in a fatal case of urosepsis. • Release of LPS has been observed after *in vitro* lithotripsy to infected artificial kidney stones. • *In vitro* application of conventional single-pulse shock waves revealed a limited bactericidal effect against bacteria in suspension and bacteria inoculated inside artificial stones. • *In vitro* application of tandem shock waves to bacterial suspensions inactivates bacteria efficiently. • *In vitro* intracorporeal lithotripsy revealed an outstanding effect against bacteria in artificial infected urinary stones. • The bactericidal effect of both extra- and intracorporeal lithotripsy should be studied carefully due the possible release of large amounts of LPS. • Under certain circumstances, this initial evidence could explain triggering of SIRS, urosepsis and MOF.

Table 1. Infected Urinary Stones, Endotoxins and Urosepsis. LPS. Lipopolysaccharide; SWL. Extracorporeal shock wave lithotripsy; SIRS. Systemic inflammatory response syndrome; MOF. Multiple organ failure.

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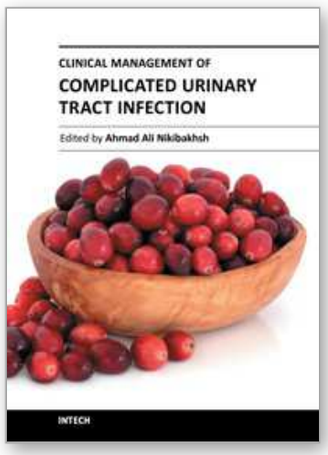

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Complicated urinary tract infections (cUTIs) are a major cause of hospital admissions and are associated with significant morbidity and health care costs. Knowledge of baseline risk of urinary tract infection can help clinicians make informed diagnostic 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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