# ROLE OF ANTIBIOTIC IN

# SHOCK-WAVE LITHOTRIPSY

by

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# ABBREVIATIONS

| | |
|---|---|
| AUA | American Urological Association |
| C&S | Culture and Sensitivity |
| CI | Confidence Interval |
| EAU | European Association of Urology |
| E. Coli | Escherichia Coli |
| ECG | Electrocardiogram |
| ESBL | Extended Spectrum Beta-Lactamase |
| ESWL | Extracorporeal Shock-Wave Lithotripsy |
| HUSM | Hospital Universiti Sains Malaysia |
| KUB | Kidney-Ureter-Bladder |
| LR | Logistic Regression |
| MRSA | Methicillin Resistant Staphylococcus Aureus |
| OR | Odds Ratio |
| RCT | Randomized Controlled Trial |
| TMP-SMX | Trimethoprim-Sulfamethoxazole |
| TMS | TechnoMed Medical System |
| URS | Ureteroscopy |
| UTI | Urinary Tract Infection |

# ABSTRAK

**Pengenalan:** Terdapat garis panduan yang bercanggah berkaitan dengan penggunaan antibiotik bagi pesakit yang menjalani kaedah rawatan Extracorporeal Shock Wave Lithotripsy (ESWL), terutama pesakit yang ujian kultur air kencing steril sebelum rawatan ESWL. Kajian ini telah dijalankan untuk menilai keberkesanan penggunaan antibiotik pada pesakit dengan jangkitan air kencing tanpa simptom dan pesakit dengan air kencing steril sebelum ESWL.

**Bahan dan Kaedah:** Dalam ujian ini, 224 pesakit dengan batu ginjal telah diperiksa dengan ujian kultur air kencing sebelum ESWL. Pesakit-pesakit ini dibahagikan kepada 2 kumpulan utama berdasarkan keputusan ujian kultur air kencing, iaitu kumpulan jangkitan air kencing tanpa simptom dan kumpulan air kencing steril. Setiap kumpulan masing-masing dirambang secara rawak kepada kumpulan intervensi (diberi antibiotik) dan kumpulan kawalan (tiada antibiotik). Ubat Ciprofloxacin 500mg diberi setengah jam sebelum ESWL kepada kumpulan intervensi. Pesakit kemudian diikuti untuk simptom jangkitan air kencing dan ujian kultur air kencing selepas satu minggu.

**Hasil:** Untuk pesakit dengan jangkitan air kencing tanpa simptom sebelum ESWL, penggunaan antibiotik mengurangkan kejadian simptom jangkitan air kencing selepas ESWL daripada 45.5% kepada 13.0% (p = 0.016). Untuk pesakit dengan air kencing steril sebelum ESWL, kejadian simptom jangkitan air kencing selepas ESWL tidak berbeza antara kumpulan intervensi dan kumpulan kawalan. Kelaziman jangkitan air kencing tanpa simptom untuk pesakit yang menjalani ESWL adalah 20.1%. Escherichia Coli adalah bakteria yang paling biasa dikultur (43.6%), diikuti oleh Klebsiella Pneumoniae (12.7%).

**Kesimpulan:** Ujian kultur air kencing rutin adalah disyorkan untuk pesakit yang dijadualkan untuk ESWL. Penggunaan antibiotik adalah disyorkan kepada pesakit dengan jangkitan air kencing tanpa simptom sebelum ESWL, kerana ia mungkin dapat mengurangkan risiko simptom jangkitan.

# ABSTRACT

**Introduction:** There are conflicting guidelines with regards to usage of antibiotic for patients undergoing Extracorporeal Shock Wave Lithotripsy (ESWL), especially for patients with sterile urine before procedure. This study was performed to evaluate the efficacy of antibiotic usage in patients with asymptomatic urinary tract infection (UTI) and in patients with sterile urine prior to ESWL.

**Materials and Methods:** In this randomized controlled trial, 224 patients with renal and ureteric stones were examined for bacteriuria (positive urine culture) prior to ESWL. These patients were classified into 2 main groups based on their urine culture result, as asymptomatic UTI group and sterile urine group. Each of these groups were then randomised to intervention (given antibiotic) group and control (no antibiotic) group. Tablet Ciprofloxacin 500mg were given half hour prior to ESWL for intervention group. Patients were then followed for symptoms of UTI and urine culture after one week.

**Results:** For patients with pre-ESWL asymptomatic UTI, antibiotic usage significantly reduced incidence of post-ESWL symptomatic UTI from 45.5% to 13.0% ($p$=0.016). For patients with pre-ESWL sterile urine, incidence of post-ESWL symptomatic UTI does not differ between intervention and control group. The prevalence of asymptomatic UTI in patients undergoing ESWL is 20.1%. Escherichia Coli was the most commonly isolated bacteria (43.6%), followed by Klebsiella Pneumoniae (12.7%).

**Conclusion:** Routine urine culture is recommended for patients scheduled for ESWL. Antibiotic usage is recommended in patients with pre-ESWL asymptomatic UTI, as it may be beneficial in reducing risk of symptomatic infection.

# 1.0 INTRODUCTION

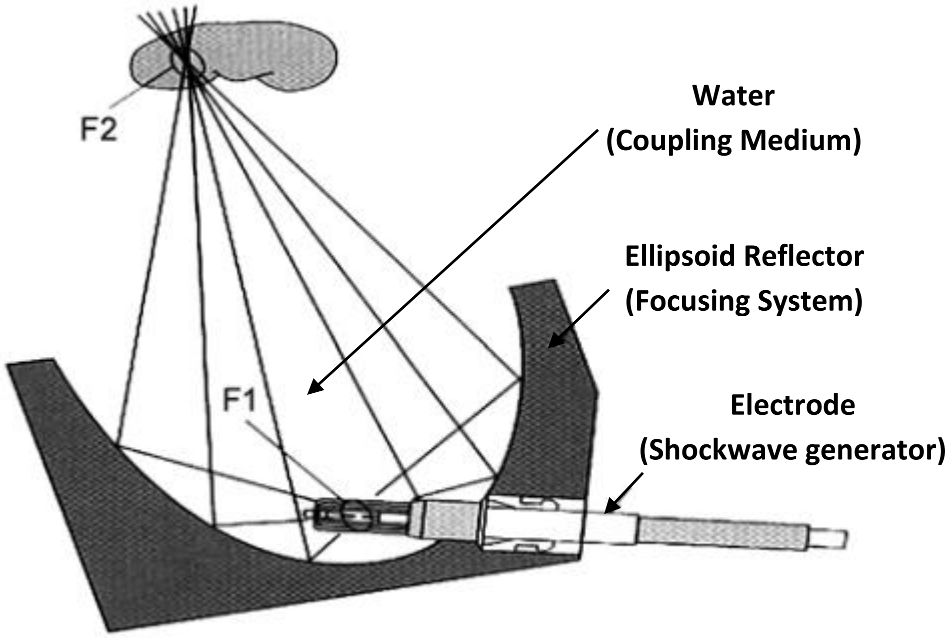
Extracorporal Shock-Wave Lithotripsy (ESWL) was first introduced in West Germany in early 1980s by Dornier Medizintechnik GmbH (now known as Dornier MedTech Systems GmbH). (Chow and Streem, 2000) This technology has since revolutionized the treatment for urolithiasis and has gained rapid acceptance worldwide because of its ease of use, minimally invasive nature and high efficacy in treating renal and ureteral stones.

## 1.1 Principles of ESWL

ESWL generates shockwave underwater (which serves as coupling mechanism), and then directed onto a focal point. The patient is positioned on a treatment table whereby the stone is localised using an imaging system. The focal point of the shockwave is positioned by moving the shockwave source or the patient. A few thousand shockwaves are generated and applied at a frequency of 60 to 120 waves per minute, resulting in treatment time of around one hour. Stone position is routinely checked using the imaging system throughout the procedure. (Köhrmann, 2005)

## 1.2 The ESWL Machine

All ESWL machines are composed of 4 essential parts – shockwave generator, focusing system, localisation system, and shockwave coupling. (Köhrmann, 2005; Andrade *et al.*, 2006):




**F1 = 1st Focal Point; F2 = 2nd Focal Point**

Fig 1: The Shockwave Machine (adapted from Andrade, 2006)

(1) Shockwave generator: The shockwave is created in the 1st focal point at the centre of an ellipsoid reflector (F1) and are directed to a second focal point (F2) inside the patient (at the stone). This focal point (F2) is the area of maximum shockwave focus. (Andrade *et al.*, 2006) There are 3 main types of generators, namely electrohydraulic, electromagnetic and piezoelectric. (Köhrmann, 2005) The ESWL machine in HUSM uses a proprietary technology called electroconductive, which is developed by EDAP-TMS in partnership with the French Medical Research Institute. (EDAP-TechnoMed, 2008)

a. Electrohydraulic generator is the original method of shockwave generation which is based on spark-gap technology. The electrode is positioned within a water-filled container. Electrical current that passes across the spark-gap electrode causes an evaporation of water bubble, which expands and immediately collapses, resulting in high pressure wave. The ellipsoid reflector focuses the shockwave to a focal point (F2), whereby it reaches high stone disintegrative capacity. (Köhrmann, 2005) However, this technology has high energy density at skin-entry point of the shockwaves which often causes pain, thereby necessitating deep sedation or anaesthesia for effective stone disintegration. (Buizza *et al.*, 1995; Köhrmann, 2005) The burning of electrodes is also not consistent, resulting in variation of different shockwaves applied in the same setting. Moreover, the electrodes need to be changed after a few treatments, resulting in higher maintenance cost of operating electrohydraulic ESWL machine. This technology is used in Dornier HM3 (Human Machine 3). (Köhrmann, 2005)

b. Electromagnetic generators use a high voltage that is applied to an electromagnetic coil, similar to loudspeakers. Electrical current that passes into the electromagnetic coil creates a transient magnetic field around the coil assembly. The magnetic field induces strong currents to the adjacent metallic membrane, which repels from the coil. Since the electromagnetic coil and metallic membrane are immersed in water, a pressure wave is formed which propagates to the parabolic focusing reflector. The parabolic reflector focuses the shockwave to a focal point (F2). The advantage of this technology is that the shockwaves produced are constant and has a smaller focal point with higher peak energy. However, this technology also causes pain, albeit lesser than electrohydraulic technology due to a smaller focal point. Example of lithotripters that utilise this technology are Dornier Doli and Lithostar Siemens. (Köhrmann, 2005; Grasso and Green, 2012)

c. Piezoelectric generators consist of multiple piezoelectric ceramic crystals set in a water-filled container. Electrical current that passes through a piezoelement stimulates alternating stress/strain changes in the material, resulting in shockwave production. These piezoelements are aligned in a hemispherical shape that directly focuses the propagation of pressure waves to a very small focal point. The resultant shockwave causes low level of pain and can be applied without sedation. The disadvantage of this technology is the need for a larger diameter of the shockwave source as well as limited total energy in the focus point. This technology is used in PiezoLith by Wolff. (Köhrmann, 2005; Grasso and Green, 2012)

Electroconductive generators are a proprietary technology developed by EDAP-TMS, tout as a fourth generation lithotripter. It is an improved technology over electrohydraulic generator whereby the patented electrode is encapsulated in a highly conductive solution (electrolyte). Electrical current that passes through the electrode produces microbubbles, that expand and collapse, generating shockwave. The shockwave generated is more consistent and the ellipsoidal reflector focuses the pressure waves to a focal point (F2). The automatic pressure regulator, incorporated within the electrode, ensures consistently higher peak energy at a small focal point. As with electrohydraulic generators, the patented electrodes need to be changed after a few treatments, which contributes to a higher operational cost. Example of lithotripter that uses this technology is Sonolith by EDAP-TMS. (EDAP-TechnoMed, 2008)

(2) <u>Shockwave focusing system</u>: This is a focusing system to direct and concentrate the shockwave energy at the stone (F2). The basic geometry of the reflector is ellipsoid. Different shockwave generators use different focusing systems. Electrohydraulic and electroconductive system uses metal ellipsoid that directs the energy created. Electromagnetic systems uses cylindrical reflector (Storz system) or acoustic lens

(Siemens system). Piezoelectric systems uses ceramic crystals arranged in a hemispherical shape. (Grasso and Green, 2012)

(3) Urinary stone imaging or localization system: There are 2 methods of localising the stone – fluoroscopy and ultrasonography. (Köhrmann, 2005)

Flouroscopy uses ionizing radiation to visualise stone. The advantage of fluoroscopy is that the stone can be visualised throughout the entire urinary tract and is easy to use. The disadvantages include usage of inonizing radiation, inability to visualise radiolucent stones, and has a higher cost of maintenance. (Grasso and Green, 2012)

Ultrasonography uses acoustic waves to localize stones. Advantages are the ability to visualise radiolucent stones and real time monitoring of procedure without ionizing radiation. However, the disadvantages are that visualisation of stone is operator dependent, small stones may be difficult to visualise and there is limitation in localising middle and lower ureter due to interposed air-filled intestinal loops. (Grasso and Green, 2012)

(4) Shockwave coupling mechanism

In transmission of wave, energy is lost at interfaces that differ in density. Therefore, a coupling system is used to minimize the loss of energy as the waves pass through the skin surface. The usual medium used is water because water has a similar density to soft tissue and is readily available. In first generation lithotripters (Dornier HM3), patients are placed in a water bath. In second, third and fourth generation lithotripters, small water-filled drums with silicone membrane are used which is in contact with patient's skin. (Grasso and Green, 2012) However, this change of ideal coupling using water bath in Dornier HM3 lithotripter to coupling cushions, necessitates the use of gel as it enables a tight bond between coupling cushions and patient's skin. As such, with the water cushion, the quality of coupling has become a critical factor that determines the success of stone fragmentation. Lower viscosity and bubble-free gel are associated with better stone fragmentation as it provides significantly better coupling quality. (Rassweiler *et al.*, 2011)

## 1.3 Evolution of Shockwave Lithotripters

Engineers at Dornier, a German Aircraft manufacturer, were studying the effects of shockwaves generated by supersonic aircraft. They observed that the shape of the aircraft could direct shockwaves onto other parts of the aircraft, accelerating metal fatigue. (Chow and Streem, 2000) In 1974, clinical research on effects of shockwave on stone disintegration was conducted between Dornier and the Ludwig Maximillians University in Munich, Germany. (Bach and Buchholz, 2011) As a result of that, the first lithotripter was produced by Dornier. In February 1980, the first patient was treated by Christian Chaussy with a prototype machine Dornier HM1 (Human Model 1) in Munich, Germany. (Chaussy *et al.*, 1982) Subsequently in 1984, Dornier launched HM3, the first commercially produced lithotripter. In this model, both patient and generator are submerged in a metal water tank. The generator is focused using the ellipsoid metal water tank. The electrodes get worn out every 200-300 shocks, and the patient had to be taken out of the water tank to change the electrodes. Despite being outdated, Dornier HM3 is still one of the most effective lithotripters and is the standard to which other newer shockwave generators are compared to. (Chow and Streem, 2000; Pes *et al.*, 2010; Grasso and Green, 2012)

Second-generation lithotripters use electromagnetic or piezoelectric generators. The coupling device has also improved into a silicon-encased water cushion that interfaced with the patient’s body. This design simplifies positioning of the patient. The advent of second generation lithotripters brought on the era of dry or tubless lithotripsy. (Winters and Macaluso Jr, 1995; Chow and Streem, 2000; Köhrmann, 2005; Pes *et al.*, 2010)

Third generation lithotripters are improvements over second-generation lithotripters in the direction of portability; integration of both fluoroscopic and ultrasonographic imaging system; and minimising pain to the patient by producing smaller focal zone. However, smaller focal zone has its own disadvantage. During respiration, the stone may move in and out of the focal zone, thus decreasing effectiveness of stone fragmentation. (Chow and Streem, 2000; Köhrmann, 2005; Pes *et al.*, 2010)

Electroconductive lithotripters are claimed by TechnoMed Medical System (TMS) as a fourth generation lithotripters. This is an improvement over electrohydraulic technology, whereby shockwaves are more consistent and electrodes last longer. (EDAP-TechnoMed, 2008)

## 1.4 Pathophysiology of Stone Fragmentation

A stone is fragmented when the shockwave force is greater than the tensile strength of the stone. Fragmentation occurs through a combination of mechanical and dynamic forces on stones such as cavitation, shearing and spalling. The most important force is thought to be cavitation. The destructive forces generated when the cavitation bubbles collapse are responsible for the ultimate stone fragmentation. (Skolarikos *et al.*, 2006)

As a shockwave is propagated through a coupling medium (water), it loses very little energy until it crosses to another medium with a different density. If the medium it crosses is denser, compressive force is produced on the new medium. If the medium is less dense, tensile stress is produced. When the wave hits the anterior surface of a stone, the change in density from low to high density produces compressive force, causing fragmentation. As the wave passes through the stone to the posterior surface of the stone, the change from high to low density produces tensile stress, again causing fragmentation. In cavitation, the negative pressure tail of acoustic pulse produces small gaseous bubbles (cavities) in the urine surrounding the stone. These bubbles immediately implode, generating powerful microjets of fluid towards the surface of the stone causing fracture of the stone. Higher shockwave rates causes greater cavitation intensity, but lowers the amplitude and duration of negative pressure in the acoustic pulse. This explains why stone fragmentation is reduced in high shockwave frequency (120 shocks per minute) as compared to low shockwave frequency (30-60 shocks per minute); and also why tissue damage increases at a high shockwave frequency. (Pes *et al.*, 2010)

## 1.5 Current Guideline on Urolithiasis

Current treatment options for renal and ureteral stones include conservative management (medical expulsion therapy), ESWL, endoscopic methods (rigid or flexible ureteroscopic lithotripsy) and percutaneous techniques (percutaneous nephrolithotomy).

European Association of Urology (EAU) guidelines on urolithiasis (Tiselius *et al.*, 2008) suggests active treatment for all urinary stones greater than 6-7mm size. For renal stone, ESWL is the first recommended option for stones ≤ 20mm. For ureteral stone, ESWL is the first treatment option for proximal ureteric stone, and in combination with ureteroscopy (URS) for middle and distal ureteric stones.

Absolute contraindications for ESWL include pregnancy, severe skeletal malformation, aortic or renal artery aneurysm, uncontrolled blood coagulopathy, and uncontrolled urinary tract infections.

## 1.6 Complications of ESWL

Complications of ESWL can be categorized into immediate complications and delayed complications.

### 1.6.1 Immediate Complications

Immediate complications are mainly related to infectious complications and effects of ESWL on tissue.

ESWL can cause trauma to thin-walled vessels in the kidneys and adjacent tissues, which result in haemorrhage, release of cytokines and inflammatory cellular mediators; and infiltration of tissue by inflammatory response cells. This may lead to short-term complications and to formation of scar; possible chronic loss of tissue function. Renal trauma and vascular disruption associated with ESWL may allow bacteria in urine to enter the bloodstream. Moreover, when infected calculi are destroyed, bacteria are released from the stone into the urine and may be absorbed systematically. (Skolarikos *et al.*, 2006).

Histopathological evaluation after ESWL in animal and human kidney showed endothelial damage to mid-size arteries, veins and glomerular capillaries. (Karlsen *et al.*, 1991; Recker *et al.*, 1992) The thin-walled arcuate veins in corticomedullary junction are especially susceptible to shockwave damage and are mainly responsible for haemorrhage, haematuria and haematoma. (Karlsen *et al.*, 1991) Although these are usually a focal process, healing in the following days, ESWL-induced acute renal damage can result in severe nephron injury, microvasculature, and surrounding interstitium. (Delvecchio *et al.*, 2003) These injuries may have long-term effect on renal function.

Gross haematuria is the most common clinical manifestation of renal trauma, which resolves in a few days. The incidence of intrarenal, subcapsular, and perirenal haematoma is reported to be around 4.1% of all post-ESWL patients. However, almost all of these patients have previously unrecognised or untreated bleeding diathesis, such as haemophilia and warfarin use. (Dhar *et al.*, 2004; Pes *et al.*, 2010) Hence, uncorrected bleeding disorders are absolute contraindication for ESWL treatment.

Cardiac arrhythmias have an incidence of 11 – 59%, usually presenting as self-limiting unifocal premature ventricular contractions.  Evidence of myocarfial injury is extremely rare. The incidence can be reduced by gating the shockwave to the electrocardiogram (ECG) pulse. (Zanetti *et al.*, 1999) Gating of shockwave refers to triggering of shockwave to the R-wave in the ECG. Ungated ESWL can still be performed, but the incidence of arrhythmia increases. (Winters and Macaluso Jr, 1995) Presence of pacemaker is not contraindication for ESWL. However, the treatment should be supervised by cardiologist. Dual-chamber pacemakers should be reprogrammed to single-chamber mode. (Albers *et al.*, 1995) Abdominal aneurysm rupture and major vein thrombosis after ESWL have been reported but is rare. (Neri *et al.*, 2000; Skolarikos *et al.*, 2006)

Gastrointestinal complications are rare and accounts for only 1.81% of post-ESWL patients in a review series. Reported complications include small bowel and colonic perforation; ureterocolic fistula; gastrointestinal anastomosis dehiscence; caecal ulcers; colonic erythema; intestinal bruising and haematomas; per rectal bleeding; pancreatitis; pancreatic haematoma and abscess formation; liver and spleen subcapsular haematomas; and ileus. (Maker and Layke, 2004)

1.6.2 Delayed Complications

Pregnancy is an absolute contraindication for ESWL because of the potential disruptive effects on the foetus, resulting in foetal damage or foetal death. (Ohmori *et al.*, 1994)

Long-term follow-up after ESWL failed to show any significant renal function impairment, even in children, when ESWL is correctly administered. (Brinkmann *et al.*, 2001; Skolarikos *et al.*, 2006)

Randomized Controlled Trials also failed to demonstrate any evidence that ESWL causes hypertension. (Jewett *et al.*, 1998; Elves *et al.*, 2000)

Evidence has showed that ESWL does not cause severe or permanent damage to testicular or ovarian function. Therefore, fertility is not affected by ESWL. (Vieweg *et al.*, 1992; Basar *et al.*, 2004)

## 2.0 LITERATURE REVIEW

ESWL is associated with remarkably few complications. One of the feared, although rare (0.1 – 1.5%), complications associated with ESWL is urosepsis, which occurs when bacteria are released from calculi as they fragmented. (Pearle and Roehrborn, 1997)

### 2.1 Role of Antibiotics in Pre-ESWL Asymptomatic UTI Patients

Every literature reviewed agrees unanimously that presence of asymptomatic UTI before ESWL is associated with higher risk of symptomatic UTI and urosepsis. The incidence of developing symptomatic UTI is 7.9% - 11%. (Matsumoto *et al.*, 2007) Therefore, antibiotics are recommended for this group of patients. However, the duration of antibiotics may differ, ranging from prophylactic dose (Matsumoto *et al.*, 2007) or duration of more than 24 hours (Wolf Jr *et al.*, 2008), depending on patient condition.

### 2.2 Role of Antibiotics in Pre-ESWL Sterile Urine Patients

The use of preoperative antimicrobial agents in high risk patients is not controversial. (Pearle and Roehrborn, 1997) High risk patients refer to patients with risk factors that predisposes a higher likelihood of developing urinary tract infection or urosepsis as compared to patients who do not have these risk factors. These risk factors are patients with infective stones; internal stent; indwelling catheter; nephrostomy tubes; history of symptomatic urinary tract infections or bacteraemia after ESWL; and those undergoing pre-ESWL endoscopic instrumentation; (Skolarikos *et al.*, 2006; Matsumoto *et al.*, 2007; Grabe *et al.*, 2009)

However, the routine use of antimicrobial prophylaxis in low risks patients with sterile preoperative urine has been widely debated. (Pearle and Roehrborn, 1997) Current guidelines across different countries cannot agree on the use of prophylaxis antibiotics prior to ESWL.

The American Urological Association's guideline on Urologic Surgery Antimicrobial Prophylaxis states that any stone manipulation including shock-wave lithotripsy increases the risk of bacteraemia. It recommends antibiotic prophylaxis in all patients undergoing shock-wave lithotripsy. The antibiotic of choice is Flouroquinolone and Trimethoprim-Sulfamethoxazole (TMP-SMX). Duration of antibiotic given is less than 24 hours. (Wolf Jr *et al.*, 2008).

European Association of Urology's Guidelines on Urological Infections states that no standard prophylaxis is recommended, except in high risks patients. This is because of the low frequency of infections after ESWL and contradictory findings on papers. It recommends TMP-SMX, $2^{nd}$ or $3^{rd}$ Generation Cephalosporin as antibiotics of choice. (Grabe *et al.*, 2009)

The Japanese Urological Association Guidelines for Prevention of Perioperative Infections in Urological Field states that for patients with pre-ESWL sterile urine, the incidence of asymptomatic bacteriuria and symptomatic UTIs after ESWL are approximately 10% (0 – 24%) and 3% (0 – 10%). Based on such evidence, possibility of clinically significant infections such as symptomatic UTIs or bacteraemia is low without antimicrobial prophylaxis. Hence, the guideline states that antimicrobial prophylaxis is not necessary for patients with pre-ESWL sterile urine, except for high risk patients. Recommended antibiotics are $2^{nd}$ generation cephalosporin or flouroquinolones. (Matsumoto *et al.*, 2007)

2.2.1 Evidence For Antibiotic Prophylaxis

Pearle et al conducted a meta-analysis and cost analysis of eight randomised controlled trials (RCTs), comparing antibiotics vs no antibiotics in patients with pre-ESWL sterile urine. In this meta-analysis, it is concluded that the use of antibiotic prophylaxis in patients with pre-ESWL sterile urine is beneficial and reduces the post-ESWL complication rate. All literatures clearly demonstrate superiority of prophylaxis over no treatment. Overall risk of developing UTI after ESWL is 2% in antibiotic group, as compared to 7% in no antibiotic group. The cost analysis shows that prophylaxis is cost-effective, provided that prophylaxis is given in the form of SMX/TMP or ciprofloxacin. Moreover, the cost of prophylactic antibiotic represents only a small fraction of the total cost of ESWL treatment. (Pearle and Roehrborn, 1997)

A large retrospective study was conducted at a Stone Clinic, Institute of Urology and Transplantation, Pakistan which spans over 17 years of experience (1990 – 2007) amounting to 21214 subjects undergoing ESWL, of which 35264 sessions of ESWL were conducted. Between the year 1990 – 2000, no antibiotic was given and the reported post-ESWL complication rate (including UTI) was 16.2%. Between the year 2001 – 2007, antibiotic prophylaxis was given, and the reported post-ESWL complication was significantly lower at 3.5%. Hence, this urology centre practises routine antibiotic prophylaxis for all pre-treatment sterile urine patients. (Hussain *et al.*, 2009)

One German RCT by Claes et al, involving 181 patients with pre-ESWL sterile urine given amoxicillin/clavulanate prior to ESWL, demonstrated significant reduction in incidence of symptomatic UTI in antibiotic group (0%) as compared to no antibiotic group (7.6%). (Claes *et al.*, 1989)

Similar findings were made by another German study. The RCT involving 50 patients with pre-ESWL sterile urine noted incidence of bacteriuria is 32% in no antibiotic group as compared to 0% in antibiotic group. This study concluded that the antibiotic Enoxacin can significantly reduce infection after ESWL. (Knipper *et al.*, 1989)

<u>2.2.2 Evidence Against Antibiotic Prophylaxis</u>

A research group in Netherland, which conducted a systemic review of 4 RCTs on ESWL, showed a fair amount of evidence that the post-ESWL rate of bacteriuria and symptomatic UTIs is low and use of antibiotic prophylaxis does not decrease this incidence. Therefore, there is no need for antibiotic prophylaxis in uncomplicated patients with pre-ESWL sterile urine. (Bootsma *et al.*, 2008)

An RCT conducted in Sweden by Petterson et al, on patients with pre-ESWL sterile urine, shows no significant difference between TMP-SMX group, Methenamine group and no antibiotic group. The study concluded that antibiotics during ESWL is unnecessary. About 30% of the patients in this study has ureteric stent. The researchers noted that patients with ureteric stent did not present with more infectious complications than those without. (Pettersson and Tiselius, 1989)

Ilker et al conducted an RCT in Turkey involving 311 patients with pre-ESWL sterile urine. Results from this study showed no significant difference between Ofloxacin group and no antibiotic group. Antibiotic prophylaxis appears to be unnecessary. However, the researchers also rational that for patients with increased risk of infection, such as infected stones, multiple large stones and perioperative urologic manipulation, prophylactic antibiotics should be used due to higher incidence of infection. (Ílker *et al.*, 1995)

Similar results were noted in a Netherland study by Bierkens et al. This RCT involving 177 patients with pre-ESWL sterile urine noted that after 2 weeks and 6 weeks post ESWL, 20% and 23% of patients developed bacteriuria. However, there is no statistical differences between antibiotic and no antibiotic group. This study concluded that antibiotic is not necessary for pre-ESWL sterile urine patients. The study was ended after interim analysis because of no differences between placebo and antibiotic prophylaxis group. (Bierkens *et al.*, 1997)

The most recent study was conducted in Iran between 2004 - 2006. This study, an RCT involving 150 patients with pre-ESWL sterile urine, showed no significant effectiveness of antibiotics on prevention of UTI after ESWL. The Post-ESWL UTI was 14% (SMX/TMP group), 10% (nitrofurantoin group) and 14% (Placebo group). (Ghazimoghaddam *et al.*, 2011)

A systemic review done in Greece based on 25 years of medline data from 1980 until 2004, concluded that the role of routine prophylactic antibiotics is controversial. While some studies show prophylaxis antibiotics demonstrate significant decrease in post-ESWL UTI, some other studies have demonstrated no advantage of prophylactic antibiotics. The study also identified pre-existing UTI, infected calculi, multiple stones, staghorn stones, history of recurrent UTIs, urinary obstruction and instrumentation at time of ESWL as predisposing factors for post-ESWL UTI. (Skolarikos *et al.*, 2006)

## 2.3 Justification for this Study

In HUSM, the current practice is no antibiotic for all patients undergoing ESWL, regardless if these patients have pre-existing bacteriuria or sterile urine prior to procedure. Urine culture is not taken prior to and after ESWL, unless patient complains of symptomatic UTI before or after procedure. This is not an uncommon practice in

Malaysia as Urology centres in Hospital Pulau Pinang, Hospital Selayang, Hospital UKM and Hospital Kuala Lumpur also do not routinely test urine for infection or give antibiotics prior to ESWL. However, there is no study in Malaysia to debate on such issue.

The low incidence of post-ESWL UTI is frequently quoted as a reason not to start antibiotics prophylaxis. However, such data applies to the western population or developed countries whereby the incidence is low around 5%. Studies in other countries such as the Middle East show a higher incidence of around 14% to as high as 16% in Pakistan. (Hussain *et al.*, 2009; Ghazimoghaddam *et al.*, 2011) The trend is higher in developing countries as compared to developed countries. This may be due to the higher rate of infective stones in developing countries. In Kelantan, the demographics of stones are 38.1% uric acid stones, 31.6% calcium oxalate stones, 27.1% struvite stones and 3.2% apatite stones. (Saiful, 2010) Hence, this study will investigate whether with antibiotic, the incidence of post-ESWL UTI can be significantly reduced in urology patients in HUSM.

### 2.4 Rationale for Using Ciprofloxacin

The most common organism encountered in a urine sample is E. Coli, followed by Klebsiella and Staphylococcus Aureus. (Nazmi *et al.*, 1997) In Malaysia, E. Coli accounts for 50.5% while Klebsiella accounts for 31.8% of bacteria isolated from urine sampling. (Williams *et al.*, 1989)

Cost-analysis shows that prophylaxis is cost-effective, provided that prophylaxis is given in the form of oral SMX/TMP or oral Ciprofloxacin. (Pearle and Roehrborn, 1997)

Foreign data report increasing resistance rates to TMP-SMX.  In a 1999 study of 202 laboratories in the US, overall resistance rates for TMP-SMX among E. Coli isolates was 16.8% (range 7.4%-33.3%) and 1.7% for ciprofloxacin. (Karlowsky *et al.*, 2001) In an interim report from 505 centres in 16 European countries, resistance to TMP-SMX among E. Coli isolates was 14.6% and 2.9% for ciprofloxacin. (Kahlmeter, 2000)

A local study done in Klang Valley by Institue of Medical Research, between August 1991 until June 1993, collected a total of 2823 specimens for analysis of antimicrobial resistance pattern. In this study, it is noted that E. Coli has 0% resistance rate to ciprofloxacin. (Cheong *et al.*, 1995)

Oral Ciprofloxacin takes 0.5 to 2 hours to achieve peak plasma concentration while oral TMP/SMX takes 1-4 hours to achieve peak plasma concentration. Hospital cost of oral ciprofloxacin is RM0.25 per tablet of 250mg strength, while oral Bactrim costs RM0.47 per tablet of 400mg strength. Choice of oral Ciprofloxacin 500mg dosage was given because it is the recommended dose for prophylaxis against UTI.

# 3.0 OBJECTIVES

## 3.1 General Objective

To determine the association between antibiotic usage and post-ESWL urinary tract infection in patients, outcome based on urine culture. Bacterial count in the urine of $10^5$ or more per ml, confirms the diagnosis of UTI.

## 3.2 Specific Objectives

(1) To compare the outcome of post-ESWL UTI between antibiotic group and no antibiotic group in patients with pre-ESWL asymptomatic UTI.

(2) To compare the outcome of post-ESWL UTI between antibiotic group and no antibiotic group in patients with pre-ESWL sterile urine.

(3) To determine the prevalence of asymptomatic UTI in patients undergoing ESWL.

## 4.0 HYPOTHESIS

### 4.1 Null Hypothesis:

There is no significant difference between antibiotic group and no antibiotic group in patients with pre-ESWL asymptomatic UTI and in patients with pre-ESWL sterile urine.

### 4.2 Alternative Hypothesis:

There is significant difference between antibiotic group and no antibiotic group in patients with pre-ESWL asymptomatic UTI and in patients with pre-ESWL sterile urine.

# 5.0 DEFINITIONS

Definitions of urinary tract infection (Teresa C. Horan and Atlanta, 2008)

a) Symptomatic Urinary Tract Infection (UTI)

   Patient has at least ONE of the following signs or symptoms with no other recognized cause: fever (>38°C), urgency, frequency, dysuria, suprapubic tenderness,

   and

   urine culture of $\geq 10^5$ microorganisms per cc of urine with no more than 2 species of microorganisms.

b) Asymptomatic bacteriuria / UTI

   Patient has no clinical evidence of infection

   and

   urine culture of $\geq 10^5$ microorganisms per cc of urine with no more than 2 species of microorganisms.

c) Sterile Urine

   No growth on urine culture

# 6.0 METHODOLOGY

## 6.1 Study Design

This is a randomised controlled trial, unblinded study.

## 6.2 Study Population / Study Period

This study included all patients who are scheduled for ESWL between 1st April 2012 until 31st December 2012 in Urology Unit, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan.

## 6.3 Inclusion Criteria

All patients with renal and ureteric stones scheduled for ESWL are included into this study

## 6.4 Exclusion Criteria

The following patients are excluded from study:

(1) Patients who has symptomatic UTI before ESWL

(2) Repeated patients for this study

(3) Patients who are allergic to ciprofloxacin

(4) Patients with recent antibiotic usage within 7 days from ESWL

## 6.5 Sample Size Calculation

### 6.5.1 Sample Size Calculation for Asymptomatic UTI Group

Sample size calculation is estimated by two proportion chi-square test using Power and Sample Size Calculations ver 3.0 by William Dupont.

(Reference: Deliveliotis, C., Giftopoulos, A., Koutsokalis, G., Raptidis, G. & Kostakopoulos, A. (1997). The necessity of prophylactic antibiotics during extracorporeal shock wave lithotripsy. International Urology and Nephrology, 29(5), 517-521)

$\alpha = 0.05$

Power = 0.8

$p_0 = 0.21$ (probability of UTI in no antibiotic group)

$p_1 = 0.02$ (probability of UTI in antibiotic prophylaxis group)

m = 1 (ratio of no antibiotic group patients to antibiotic prophylaxis group patients)

n = 43 per group

Total n = [n x 4] + 10% (lost to follow-up) = 190

**Total sample size (n) needed: 190**

6.5.2 Sample Size Calculation for Sterile Urine Group

Sample size calculation is estimated by two proportion chi-square test using Power and Sample Size Calculations ver 3.0 by William Dupont.

(Reference: Knipper, A., Böhle, A., Pensel, J. & Hofstetter, A. (1989). Antibiotic prophylaxis with enoxacin in extracorporeal shockwave lithotripsy. Infection, 17, S37-S38.)

$\alpha = 0.05$

Power = 0.8

$p_0$ = 0.32 (probability of UTI in no antibiotic group)

$p_1$ = 0.02 (probability of UTI in antibiotic prophylaxis group)

m = 1 (ratio of no antibiotic group patients to antibiotic prophylaxis group patients)

n = 23 per group

Total n = [n x 4] + 10% (lost to follow-up) = 102

**Total sample size (n) needed: 102**

6.5.3 Sample Size Calculation for Prevalence of Asymptomatic UTI

Sample size calculation is estimated by single proportion equation using EpiInfo ver 6.

(Reference: Skolarikos, A., G. Alivizatos, et al. Extracorporeal shock wave lithotripsy 25 years later: complications and their prevention. European urology 2006; 50(5): 981-990.)

Expected prevalence: 23.5%

Worst acceptable prevalence: 30%

With Confidence Interval of 95%, a sample size of 163 is required.

Total n = n + 10% (loss to follow-up) = 180

**Total sample size (n) needed: 180**

In conclusion, the **minimum sample size needed for this study is 190** (based on calculation of sample size for asymptomatic bacteriuria)