

Review on the outpatient treatment for pelvic inflammatory disease, what is the best for Hong Kong?

評論什麼是最適合香港的盆腔炎門診治療方法？

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Pelvic inflammatory disease is an important risk factor for infertility, ectopic pregnancy and chronic pelvic pain. Although the Centers for Disease Control and Prevention published treatment guidelines for pelvic inflammatory disease in 2002, the effectiveness of treatment has been affected by the emergence of quinolone-resistant *Neisseria gonorrhoeae*. The prevalence of quinolone-resistant *Neisseria gonorrhoeae* is highly variable with time and place. In Hong Kong, quinolone-resistant *Neisseria gonorrhoeae* is over 90%, thus ceftriaxone, doxycycline and metronidazole should be the treatment of choice. For patients sensitive to cephalosporins, azithromycin and metronidazole can be considered as alternative treatments. (*Hong Kong j.emerg.med.* 2005; 12:162-167)

盆腔炎是不育、宫外孕及慢性盆腔痛症的一個重要風險因素。雖然美國疾病控制及預防中心於 2002 年出版了治療盆腔炎的指引，但治療的功效因抗喹諾酮淋病球菌的出現而受到影響。抗喹諾酮淋病球菌的流行程度因時間及地點而極之反覆不定。在香港，抗喹諾酮淋病球菌達九成以上，故應選擇頭孢曲松、多西環素及甲硝唑治療。如病人對頭孢菌素類有敏感，可以考慮阿紅霉素及甲硝唑作替代治療。

Keywords: Azithromycin, ceftriaxone, drug resistance, drug therapy, metronidazole

關鍵詞：阿紅霉素、頭孢曲松、抗藥性、藥物治療、甲硝唑

Introduction

Pelvic inflammatory disease (PID) is inflammation and infection of the upper genital tract in women, typically involving the fallopian tubes, the ovaries, and the surrounding structures.¹ The pathogens most commonly involved are *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. The normal vaginal flora including streptococci, *Escherichia coli*, *Haemophilus influenzae* and anaerobes such as *Bacteroides*,

Peptostreptococcus and *Peptococcus* often contribute. PID increases the risk of infertility (x 10)² and ectopic pregnancy (x 2-10).^{3,4} One-fifth of chronic pelvic pain is related to PID.⁵

There is no single historical, physical or laboratory finding which is both sensitive and specific for the diagnosis of PID. Thus, PID is difficult to diagnose. Clinical diagnosis of symptomatic PID has a 65-90% positive predictive value for salpingitis. On the other hand, the endocervical swab may not pick up infection within the uterus. So, treatment solely based on its result will not only delay the treatment, but may result in inappropriate or inadequate treatment.

In view of this, we need a standardised diagnosis and treatment guideline for PID basing on the local

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bacteriology and antibiotic resistance pattern in Hong Kong. According to the Centers for Disease Control and Prevention (CDC) Guidelines 2002,⁶ empiric treatment of PID should be initiated in sexually active young women and other women at risk for sexually transmitted diseases if the "minimum criteria" are present and no other cause(s) for the illness can be identified. The "minimum criteria" are uterine/adnexal tenderness or cervical motion tenderness. Additional criteria may be used to enhance the specificity of the minimum criteria. Additional criteria that support a diagnosis of PID include the followings: -

- Oral temperature >101°F (>38.3°C);
- Abnormal cervical or vaginal mucopurulent discharge;
- Presence of white blood cells (WBC) on saline microscopy of vaginal secretions;
- Elevated erythrocyte sedimentation rate;
- Elevated C-reactive protein; and
- Laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*.

The most specific criteria for diagnosing PID include the followings: -

- Endometrial biopsy with histopathologic evidence of endometritis;
- Transvaginal sonography or magnetic resonance imaging techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex; and
- Laparoscopic abnormalities consistent with PID.

Besides, the CDC also suggested the following admission criteria for PID: -

- Surgical emergencies (e.g., appendicitis) cannot be excluded;
- The patient is pregnant;
- The patient does not respond clinically to oral antimicrobial therapy;
- The patient is unable to follow or tolerate an outpatient oral regimen;
- The patient has severe illness, nausea and vomiting, or high fever; and the patient has a tubo-ovarian abscess.

For outpatient treatment, there are two regimes available: -

Regimen A: Ofloxacin 400 mg orally twice a day for 14 days OR Levofloxacin 500 mg orally once daily for 14 days WITH or WITHOUT Metronidazole 500 mg orally twice a day for 14 days.

Regimen B: Ceftriaxone 250 mg intramuscularly (IM) in a single dose OR Cefoxitin 2 g IM in a single dose and Probenecid 1 g orally administered concurrently in a single dose OR other parenteral third-generation cephalosporins (e.g., cefuroxime or cefotaxime) PLUS Doxycycline 100 mg orally twice a day for 14 days WITH or WITHOUT Metronidazole 500 mg orally twice a day for 14 days.

The role of metronidazole

The PID guideline 2002 from CDC 2002 downgraded the importance of antibiotic cover for the anaerobes when treating PID.⁷ Metronidazole was used as an optional treatment only. These changes reflected the high short-term efficacy of regimens even without anaerobic coverage.^{8,9} There is no hard evidence that inadequate anaerobic coverage leads to suboptimal outcomes. However, in clinically severe diseases,¹⁰ particularly in the presence of a tubo-ovarian abscess,¹¹ anaerobic cover should still be used.

In addition, anaerobes constitute a significant proportion of bacteria isolated in patients with PID – 26.4% in the Queen Mary Hospital (QMH) Hong Kong study in 1996,¹² 37.7% in the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) study in the United States in 1996-1999,¹³ 26.3% in an Indian study in 2003.¹⁴ Anaerobes can cause tissue damage to the fallopian tubes, either directly or indirectly through the host inflammatory response.¹⁵ Salpingitis causes tubal scarring with resultant tissue damage, which may both interfere with ovum transport and cause chronic pelvic pain.¹⁶ It should be understood that both ceftriaxone and doxycycline have minimal anaerobic coverage. Although there is no good study documenting the usefulness of metronidazole in the empirical treatment of PID, metronidazole should be added from the pathophysiological point of view.

Quinolone-resistant *Neisseria gonorrhoeae* (QRNG)

In the PEACH study in the United States,¹⁷ *Neisseria gonorrhoeae* was found in 21% of patients with PID. In the QMH study from Hong Kong, it was found in 25% of patients with PID.¹² QRNG has great geographic and temporal variations. It is common in Asia, the Pacific Islands, California and England. From the Gonococcal Isolate Surveillance Programme in CDC on 26 April 2004,¹⁸ the prevalence of QRNG was 9.8% in England and Wales, and 8.1% in Australia. However, in China, the QRNG prevalence was 92.5%. In Hong Kong, an alarming rise in QRNG prevalence has been observed. It was found to be 0% in 1987-1990,¹⁹ 0.5% in 1992, 10.4% in 1994,²⁰ 24% in 1996, 50% in 1998 and 94% in 2000.^{21,22} Therefore the regime A suggested by the CDC would not be a good choice in the treatment of PID in Hong Kong. In the CDC 2004 guideline,²³ ceftriaxone 125 mg IM or cefixime 400 mg orally are the main treatment for QRNG. Spectinomycin 2 g IM is an alternative. However, Cefixime is not available and Spectinomycin is not easily accessible in public hospitals in Hong Kong.

Neisseria gonorrhoeae were all sensitive to third generation cephalosporins in the study in the Western Pacific Region by the World Health Organization in 1996.²⁴ In a study in Japan in 2002, all *Neisseria gonorrhoeae* were sensitive to ceftriaxone.²⁵ The study done in Hong Kong in 1992-1995 showed all QRNG were sensitive to ceftriaxone and spectinomycin.²⁶ The study done by the Prince of Wales Hospital in 2000 showed that all *Neisseria gonorrhoeae* were sensitive to ceftriaxone and 85% of them were sensitive to spectinomycin.²² In 2003, data from the Department of Microbiology, Tseung Kwan O Hospital also showed that all *Neisseria gonorrhoeae* were sensitive to ceftriaxone. Therefore, ceftriaxone should be included in the treatment of gonococcal infection and PID in Hong Kong.

Patient with cephalosporin allergy

Azithromycin has a role in the management of QRNG and PID. In a multicentre trial done in 1994,²⁷ a single dose of azithromycin 2 g was found to be equally

effective as ceftriaxone in the treatment of uncomplicated gonococcal infection. However, it was associated with a higher frequency of gastrointestinal side effects and was more expensive. For uncomplicated genital chlamydial infection, azithromycin 1 g has been shown to be equally effective as a standard dose of doxycycline 100 mg orally twice daily for 7 days.^{28,29} In 2003, the Department of Health Services of California suggested azithromycin 2 g orally in a single dose as an alternative in QRNG.³⁰ In 2004, the Department of Health and Mental Hygiene of New York suggested azithromycin 2 g orally in a single dose as an alternative in QRNG.³¹ In 2003 India,³² a single dose of azithromycin 1 g, fluconazole 150 g and secnidazole 2 g was found to be effective (cure rate of 93.5%) in PID.

In 2003, a study from the United Kingdom showed that azithromycin with or without metronidazole was an effective regime in PID.³³ They used azithromycin 500 mg intravenously for 1-2 days followed by 250 mg daily orally for a total of 7 days, with or without metronidazole 400 mg or 500 mg intravenously 3 times daily, then orally for a total of 12-14 days.

Azithromycin has special pharmacokinetic properties.³⁴ It has a long elimination half-life of more than 50 hours. The drug is concentrated within the phagocytic cells and tissues and it achieves targeted delivery by these cells to the site of infection. The uptake of azithromycin into the inflammatory cells is both concentration-dependent and non-saturable. So the administration of higher doses of the drug early in the infection, when the inflammatory response is most pronounced, should result in increased concentrations of drug within the inflammatory cells recruited to the sites of infection.

Comparing with the regime using ceftriaxone plus doxycycline plus metronidazole, the regime using azithromycin plus metronidazole does not need intramuscular injection. It will likely lead to better patient compliance to treatment because of simplicity. The regime using ceftriaxone has been proved to be effective in the treatment of PID and adopted by the CDC Guidelines 2002 but up to now, there were only two studies using azithromycin in PID.

In conclusion, azithromycin 2 g single dose orally can cover both gonococcus and chlamydia, and can be used in the treatment of PID. However, up to now, there is no international commonly agreed regimen for the use of azithromycin in the treatment of PID. The exact regimen of azithromycin in the treatment of PID in Hong Kong needs further study.

Conclusions

In the treatment of PID, CDC guidelines could be followed. PID increases the risk of infertility,

ectopic pregnancy and chronic pelvic pain. In areas with a high prevalence of quinolone-resistant *Neisseria gonorrhoeae*, for example Hong Kong and China, ceftriaxone 250 mg IM, plus doxycycline 100 mg orally twice a day for 14 days, with or without metronidazole 400 mg orally three times a day for 14 days is recommended. In case of cephalosporin allergy, azithromycin 2 g orally once may be used to cover *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Appropriate investigations, drug compliance, follow-up arrangement, tracing and advice on sexual partner are also important for effective treatment (Appendix).

Appendix.

Suggested regime of outpatient treatment of pelvic inflammatory disease in Hong Kong

i. Diagnosis

The minimal criteria are

- Uterine/adnexal tenderness or
- Cervical motion tenderness.

The additional criteria are

- Oral temperature >101°F (>38.3°C);
- Abnormal cervical or vaginal mucopurulent discharge;
- Presence of white blood cells on saline microscopy of vaginal secretions;
- Elevated erythrocyte sedimentation rate;
- Elevated C-reactive protein;
- Laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*.

ii. Initiation

Start treatment in Emergency Department if sexually active women

- plus Minimum criteria present
- plus No other causes for the illness identified
- plus Absence of admission criteria

iii. Investigation

Endocervical swab for culture and sensitivity test

- plus *N. gonorrhoeae*
- plus *C. trachomatis* (special medium)

iv. Antibiotic regime

Ceftriaxone 250 mg intramuscularly

plus

Doxycycline 100 mg orally twice daily for 14 days

with or without

Metronidazole 400 mg orally 3 times daily for 14 days

If cephalosporin allergy, consider azithromycin 2 g orally once

with or without

Metronidazole 400 mg orally three times daily for 14 days

v. Follow-up in Gynaecology Clinic, Emergency Department or Social Hygiene Clinic

vi. Others

- Removal of intrauterine contraception device,
- Sexual partner advice and Social Hygiene Clinic referral

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