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REVIEW ARTICLE

Role of moxifloxacin for the treatment of commmunity-acquired complicated intra-abdominal infections in Taiwan

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Complicated intra-abdominal infections (cIAIs) are common yet serious infections that can potentially lead to substantial morbidity and morbidity. As an essential adjunct to source control, the goals of antimicrobial therapy are to promote patient recovery, reduce recurrence risk, and prevent antimicrobial resistance. The current international guidelines on the

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Complicated intra-abdominal infections;
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empirical treatment of community-acquired complicated IAIs were published by the Infectious Diseases Society of America (IDSA) and Surgical Infections Society (SIS) in 2010. These guidelines all recommend the use of a fluoroquinolone (ciprofloxacin or levofloxacin) plus metronidazole for mild-to-moderate- and high-severity cases. Moxifloxacin monotherapy is recommended by the current IDSA/SIS guidelines for the treatment of mild-to-moderate complicated IAIs. Moxifloxacin has demonstrated a broad spectrum coverage of both aerobic and anaerobic pathogens, good tissue penetration into the gastrointestinal tract, and a good tolerability profile. Clinical data have demonstrated that moxifloxacin is at least as effective as other standard therapeutic regimens recommended by current clinical guidelines. Due to the high rates of extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* and fluoroquinolone-resistant *Enterobacteriaceae* among isolates causing community-acquired IAIs in Asia, any fluoroquinolones (including moxifloxacin) are not recommended as drugs of choice for the empirical treatment of community-acquired IAIs, particularly in countries (China, India, Thailand, and Vietnam) with fluoroquinolone resistance rates among *Escherichia coli* isolates of >20%. Given the low rates of fluoroquinolone-resistant (<20%) and extended-spectrum β-lactamase (ESBL)-producing (<10%) *Enterobacteriaceae* isolates associated community-acquired IAIs in Taiwan, it appears that moxifloxacin is considered an appropriate first-line therapy for patients with community-acquired complicated IAIs in this country.

Introduction

Community-acquired complicated intra-abdominal infections (cIAIs) are common in clinical practice and are associated with substantial morbidity and mortality and healthcare burden.[1–4] These infections can be managed effectively through patient stabilization, source control (surgical debridement, drainage, and repair), and appropriate antimicrobial therapy.[5] The goals of antimicrobial therapy are to promote patient recovery, reduce recurrence risk, and prevent antimicrobial resistance.[1–5] The current international guidelines on the empirical treatment of community-acquired complicated IAIs were established in 2010 by the Infectious Diseases Society of America (IDSA) and Surgical Infections Society (SIS), and the consensus on antimicrobial therapy of intra-abdominal infections in Asia.[1–3] IDSA and SIS guidelines both recommended use of a fluoroquinolone (ciprofloxacin or levofloxacin) plus metronidazole for mild-to-moderate- and high-severity cases. Moxifloxacin monotherapy is recommended by the current IDSA for the treatment of mild-to-moderate complicated IAIs.[1,2] However, due to the high rates of extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* and fluoroquinolone-resistant *Enterobacteriaceae* among isolates causing community-acquired IAIs in Asia, any fluoroquinolones (including moxifloxacin) are not recommended as drugs of choice for empirical treatment of community-acquired IAIs, particularly in countries (China, India, Thailand, and Vietnam) with fluoroquinolone resistance rates among *Escherichia coli* isolates of >20%.[3]

This paper reviews the epidemiology and antimicrobial resistance status among pathogens associated with IAIs and summarizes the clinical and bacteriological evidences regarding the use of moxifloxacin as monotherapy therapy for the treatment of community-acquired cIAIs in Taiwan.

Definitions of intra-abdominal infections

Intra-abdominal infections (IAIs) are caused by the multiplication of pathogenic microorganisms within the normally sterile environment of the abdomen.[1] They can be classified as uncomplicated or complicated. Although IAIs are not uncommon following operative procedures or during hospital stay, most of these infections (~80%) are community-acquired.[1,6]

Uncomplicated infections typically involve only a single organ without anatomical disruption. Typical examples are acute cholecystitis, acute diverticulitis, and acute appendicitis.[7] These infections are often managed successfully with surgical resection alone without the extensive use of antibiotics, except for preoperative prophylaxis. Depending on the disease rapidity and appropriateness of treatment, uncomplicated IAIs may progress to cIAIs.[8]

However, cIAIs involve infections that extend beyond the organ of origin and into the peritoneal space. Clinically, complicated appendicitis and diverticulitis are the most frequently encountered cIAIs and are the predominant reasons for emergency department visits due to acute abdomen. They are associated with secondary peritonitis or abscess formation and require source control procedures and concomitant parenteral antimicrobial therapy.[1,9,10] Secondary peritonitis is characterized by the presence of polymicrobial infection resulting from the disruption of the gastrointestinal tract or extension of an existing intra-abdominal infection. While secondary peritonitis is predominantly caused by gram-negative aerobes and gram-positive cocci, abscess formation is predominantly due to anaerobes.[8,11]

Etiologies of cIAIs in Taiwan

A variety of aerobic and anaerobic pathogens are responsible for the pathogenesis of cIAIs in Taiwan (Fig. 1).

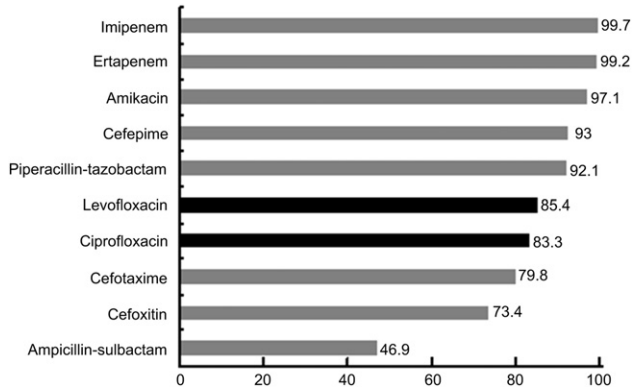

Figure 1. *In vitro* susceptibility of 10 antimicrobial agents against 610 isolates of *Enterobacteriaceae* recovered from patients treated at seven hospitals in Taiwan in 2009. Data were derived from Study for Monitoring Antimicrobial Resistance Trends (SMART).[14]

Overall, the most common pathogens are aerobic *Enterobacteriaceae* especially *E coli*, and obligate anaerobes, such as *Bacteroides fragilis*.[12] The presence of specific pathogens depends on the origin of the infection.[1] While gram-positive and gram-negative aerobic and facultative pathogens are commonly isolated from the stomach, duodenum, biliary tract and proximal small bowel, gram-negative facultative and aerobic organisms and obligate anaerobes are frequently the isolates from the distal small bowel. Colon-derived infections, however, are typically associated with facultative or obligate anaerobic organisms.[6,9,10]

Initiated in 2002, the Study for Monitoring Antimicrobial Resistance Trends (SMART) was designed to globally monitor the longitudinal trends in epidemiology and *in vitro* antimicrobial susceptibility of aerobic and facultative gram-negative bacilli (GNB) isolated from patients with IAIs.[13] Results peculiar to Taiwan have been published separately or along with other Asia-Pacific countries.[14,15] From 2002—2006, among 492 aerobic and facultative anaerobic GNB isolates collected from patients with IAIs at the National Taiwan University Hospital, *Enterobacteriaceae* comprised 68.3% of all isolates, of which *Klebsiella* spp. (26.2%) was the commonest, followed by *E coli* (24.8%), *Enterobacter* spp. (7.3%), and *Aeromonas hydrophila* (7.1%).[15] Among glucose nonfermentative GNB, the common pathogens were *Acinetobacter baumannii* (9.3%) and *Pseudomonas aeruginosa* (7.1%).

Antimicrobial resistance profiles of pathogens associated with IAIs in Taiwan

The SMART data on 2009 from seven medical centers in Taiwan revealed the susceptibility rates of IAI-related *Enterobacteriaceae* isolates (n = 610) to levofloxacin (85.4%) and ciprofloxacin exceeded 80% (Fig. 1).[14] Among 610 *Enterobacteriaceae* isolates, the rates of extended-spectrum β-lactamase (ESBL)-producing *E coli* and *Klebsiella pneumoniae* were 7.5% and 7%, respectively.[14] The ESBL rates were lower among isolates (3.6% for *E coli* and 2.4% for *K pneumoniae* isolates) recovered from patients admitted within 48 h (presumptive community-acquired) than those from patients hospitalized for more than 48 h.

Data from five SMART consistent participating hospitals in Taiwan also showed low rates of ESBL-producing *E coli* (4.9%) and *K pneumoniae* (3.7%) for community-acquired isolates (admitted within 48 h) (Fig. 2A). More than 80% of

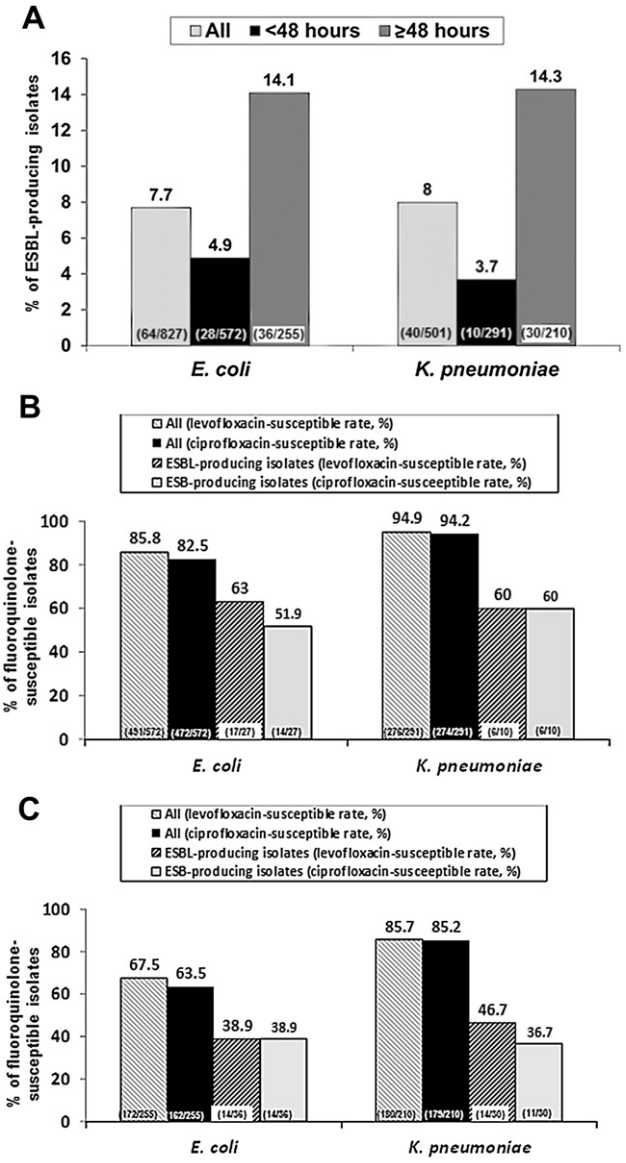

Figure 2. Rates of extended-spectrum β-lactamase (ESBL)-producing *Escherchia coli* and *Klebsiella pneumoniae* isolates recovered from patients (within or ≥48 h of admission) with intra-abdominal infections (IAIs) who were treated at five hospitals in Taiwan that consistently participated in Study for Monitoring Antimicrobial Resistance Trends (SMART) program from 2006 to 2010 (A). Susceptibility rates to levofloxacin or ciprofloxacin among *E. coli* and *K. pneumoni*ae isolates, collected within 48 h (B) and ≥48 h (C) of hospitalization, causing presumptively community-acquired IAIs at the five hospitals in Taiwan in from 2006 to 2010. Data were derived from the Study for Monitoring Antimicrobial Resistance Trends (SMART).

community-acquired *E coli* and >90% of community-acquired *K pneumoniae* isolates were susceptible to ciprofloxacin and levofloxacin. About 50—60% of community-acquired ESBL-producing *E coli* and *K pneumoniae* isolates were susceptible to ciprofloxacin and levofloxacin, although the rates of ESBL production among these community-acquired isolates was low (<5%).

Moxifloxacin exhibited good antimicrobial activity (minimum inhibitory concentrations [MICs], ≤2 μg/mL) against both aerobic (90.8%) and anaerobic (97.1%) pathogens from patients with IAIs and diabetic foot infections.[16] A study of susceptibilities of bacterial isolates from patients with IAIs at a medical center in Taiwan during the period 2001 to 2006 showed that more than 85% of *Enterobacteriaceae* were susceptible to moxifloxacin.[17] Overall, the *in vitro* activities of moxifloxacin were better than those of ciprofloxacin and levofloxacin.[17]

Data on *in vitro* susceptibility of anaerobes associated IAIs to fluoroquinolones are lacking in Taiwan. Liu et al reported antimicrobial susceptibility of 207 nonduplicate anaerobic blood isolates which revealed that 90% of the isolates were susceptible to moxifloxacin (Fig. 3A).[18] Moxifloxacin also exerted potent activity (about 90%) against all *Bacteroides* species, the main gram-negative anaerobic bacteria causing IAIs (Fig. 3B).[18]

Principles of antimicrobial therapy for cIAIs

Antimicrobial therapy is not a substitute for but an essential adjunct to source control in the management of cIAIs.[5] Its goals are to eliminate pathogenic organisms remaining after source control procedures, thereby promoting recovery and reducing the risk of recurrence.[1] Treatment failure in patients with cIAIs is due to inadequate source control and/or inadequate antimicrobial coverage, which is potentially due to the presence of resistant organisms.

Treatment success is closely linked to the appropriate choice of empiric therapy. A study of initial empiric therapy in patients with community-acquired cIAIs showed that nearly 80% of the patients receiving an appropriate antibiotic regimen were successfully treated, whereas 47% of those receiving inappropriate therapy failed initial therapy.[19]

Data on the clinical microbial epidemiology and susceptibilities provide invaluable information for determining appropriate antimicrobial regimens for empiric therapy, thereby reducing the risk of development of inappropriate therapy-related resistance. These were consistent with the recommendations proposed by the IDSA and SIS for the initial empiric treatment of cIAIs.[1,2] Of note, aminoglycoside-based regimens are not advocated as the first-line treatment for cIAIs due to their increased toxicities and inferior efficacy compared to other agents. Likewise, because of the widespread emergence of resistance, ampicillin/sulbactam is no longer recommended for use in the treatment of patients with cIAIs.

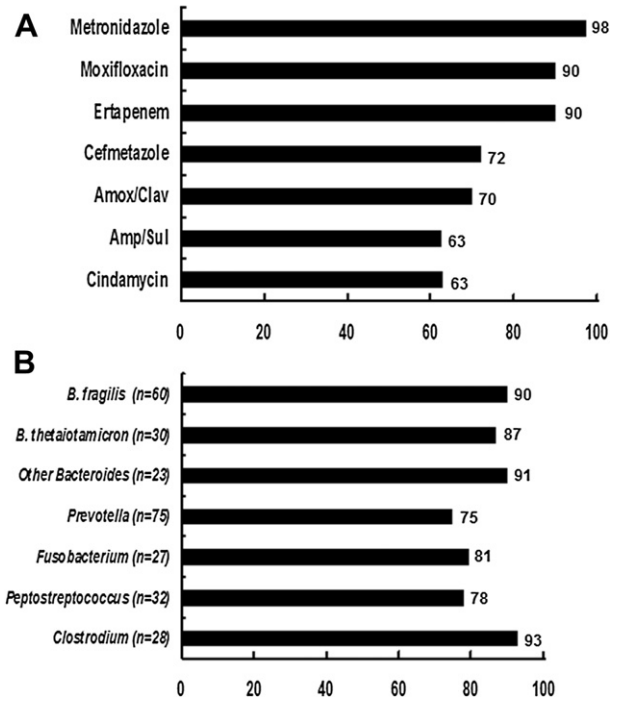

Figure 3. (A) *In vitro* susceptibility of moxifloxacin and other six antimicrobial agents against 207 blood isolates of anaerobes (A) and against different species of anaerobes (B) recovered from patients treated at national Taiwan University Hospital from 2006 to 2007.[24]

Role of moxifloxacin in the treatment of cIAIs

Due to increasing bacterial resistance, there is an ongoing need for additional antimicrobial agents for the management of cIAIs.[12] Moxifloxacin is a fluoroquinolone with a broad spectrum of activity against both aerobic and anaerobic bacteria and has been recommended as a first-line monotherapy for the empiric treatment of cIAIs.[1] Moxifloxacin can be administered as a once-daily monotherapy regimen and does not require a dosage adjustment in patients with impaired renal function. Moxifloxacin is available in both oral and intravenous formulations at the same dosage, providing flexibility to switch from the parenteral to the oral route of administration while maintaining effective on-site concentrations.

Although fluoroquinolones share similar mechanisms of action, there are important differences in their pharmacological and bactericidal properties. Moxifloxacin has a relatively greater bioavailability, longer half-life, and higher peak serum concentration (Cmax) than ciprofloxacin.[20] In the context of cIAIs, moxifloxacin has a high penetration and accumulation into the gastrointestinal mucosa in preoperative patients awaiting gastrointestinal surgery.[21] After intravenous (IV) administration, moxifloxacin concentrations achieving in abdominal tissue, abdominal exudate, and abscess fluid were above the MIC_{90} values for key pathogens commonly encountered in patients with cIAIs, such as *E coli* and *Bacteroides fragilis*.[22—24]

Clinical efficacy of moxifloxacin for the treatment of IAIs

There were four Phase III clinical trials using moxifloxacin and other comparator antibiotics for the treatment of IAIs (Table 1).[12,25—27] Randomized clinical studies have

Table 1 Summary of clinical trials on the efficacy of moxifloxacin and comparator antibiotics for treatment of community-acquired intra-abdominal infections

Author, year of study [reference]	Study design	Study agents		Duration (days)	% (no. of patients with indicated outcome/ no. of patients enrolled)	
		Comparator antibiotics	Moxifloxacin (400 mg, qd)		Clinical success moxifloxacin/ comparator	Bacteriological eradication moxifloxacin/comparator
Malangoni et al 2000–2003[12]	Double-blind, controlled	IV piperacillin/tazobactam (3.0/0.375 g tid) followed by PO amoxicillin/clavulanate (800/114 mg bid)	IV/PO	5–14	80 (124/156)/82 (136/165)	78 (117/150)/77 (126/163)
Weiss et al 2001–2002[25]	Open, controlled	IV ceftriaxone (2 g qd) and IV metronidazole (500 mg tid) followed by PO amoxicillin/ clavulanate (500/125 mg tid)	IV/PO	5–14	80.9 (199/246)/82.3 (218/265)	77.7 (262/337)/80.7 (293/363)
Solomkin et al 2005–2007[26]	Double-blind, controlled	IV ceftriaxone (2 g qd) and IV metronidazole (500 mg bid)	IV	3–14	90.2 (157/174)/96.5 (165/171)	89.4 (118/132)/95.9 (118/123)
De Waele et al 2006–2009[27]	Double-blind, controlled	IV ertapenem (1 g qd)	IV	5–14	89.4 (312/349)/93.4 (323/346)	86.5 (257/297)/90.2 (249/276)

IV = intravenous; PO = per os.

demonstrated the safety and efficacy of initial moxifloxacin monotherapy in patients with cIAIs. Sequential therapy with IV to oral once-daily moxifloxacin was safe and well tolerated, and as efficacious as a multi-dose regimen of IV piperacillin/tazobactam followed by oral amoxicillin/clavulanic acid.[12] The overall clinical cure rate (per protocol analysis) was 80% with moxifloxacin and 78% with the comparator.

In another study, sequential moxifloxacin monotherapy was demonstrated to be as effective and safe as combination therapy with IV ceftriaxone plus IV metronidazole followed by oral amoxicillin/clavulanic acid for the treatment of cIAIs, with a clinical cure rate of 80.9% which was noninferior to that (82.3%) of the comparator regimen (moxifloxacin vs. comparator; 95% confidence interval [CI], −8.9 to 4.2).[25] The incidence of adverse events was comparable between the two treatment groups. Consistent results were observed in an Asian study which compared IV moxifloxacin monotherapy versus IV ceftriaxone plus IV metronidazole, without oral switch-down in both groups.[26] Moxifloxacin was noninferior to the comparator with clinical cure rate of 90.2% and 96.5%, respectively (95% CI, −11.7 to −1.7).

Moxifloxacin was also clinically noninferior to ertapenem, both administered as IV monotherapy, for the treatment of cIAIs.[27] The primary analysis of a multinational trial showed that moxifloxacin was significantly noninferior to ertapenem (cure rate of 89.5% vs 93.4%; 95% CI, −7.9 to 0.4). Similar responses between treatments at test-of-cure were seen for the different types and causes of infection, with the highest response rate for localized peritonitis (93.0% with moxifloxacin vs. 93.8% with ertapenem) and for cholecystitis (100.0% vs. 96.9%), respectively. The incidence of drug-related adverse events was similar across both treatment groups (18.9% vs. 19.0%).[27]

A pooled analysis of four randomized clinical trials reported from 2000 to 2010 investigated the comparative efficacy of moxifloxacin in the treatment of cIAIs, including infection with anaerobic organisms.[28] The overall clinical success rates in the per protocol population were 85.6% for moxifloxacin and 87.8% for comparator antibiotics. More than 87% of baseline anaerobic isolates from IAIs were susceptible to moxifloxacin (MIC of $\leq$2 μg/mL). The overall clinical success rate of moxifloxacin for all anaerobes was 82.3%. The efficacy remained >80% for anaerobic isolates with MICs of 4–16 μg/mL beyond the current susceptibility breakpoint MIC of $\leq$2 μg/mL against major anaerobes.[28]

In the treatment of patients with community-acquired cIAIs, high rates of treatment success can be achieved by the appropriate selection of antibiotics. Moxifloxacin is a fluoroquinolone with a broad spectrum of activity against both aerobic and anaerobic bacteria, providing sufficient coverage against bacterial isolates from patients with community-acquired IAIs in Taiwan. It achieves high penetration and accumulation into gastrointestinal mucosa, abdominal exudate, and abscess fluid and appears to be as clinically effective as other standard therapeutic regimens recommended by current clinical guidelines. Clinical data are now available to support its efficacy in patients with community-acquired cIAIs. Moxifloxacin has been approved for use in Taiwan as monotherapy to treat intra-abdominal infections, among other indications. Given the relatively

low frequencies of ESBL-producing isolates, it appears that moxifloxacin is an appropriate first-line therapy for patients with community-acquired complicated intra-abdominal infections in Taiwan.

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