

Early-onset septicemia due to CMY-2-producing *Escherichia coli* in a woman with blunt abdominal trauma

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Received: May 1, 2008 Revised: August 11, 2008 Accepted: September 25, 2008

Escherichia coli remains one of the most common etiologies of secondary peritonitis. CMY-2 is the most prevalent AmpC enzyme identified in nosocomial *E. coli* isolates causing bacteremia in Taiwan. This report is of a patient who underwent surgery for intestinal perforations due to blunt abdominal trauma and developed unexpected CMY-2-producing *E. coli* septicemia in the early postoperative period. The AmpC-type CMY-2 enzyme might partially contribute to the poor response to antimicrobial therapy of amoxicillin-clavulanic acid or flomoxef. Late changes in antibiotic therapy to an appropriate regimen of ceftazidime based on the culture results did not result in a positive outcome and the patient died. Whether selection of an anti-AmpC regimen is appropriate as first-line treatment for traumatic abdomen-associated septicemia should be an area of further investigation in Taiwan.

Key words: AmpC beta-lactamases; beta-lactamase CMY-2; *Escherichia coli*; Peritonitis

Introduction

Postoperative peritonitis is a major problem, with an incidence of 39.4% after blunt traumatic rupture of the small bowel [1]. *Escherichia coli* is the most common causative pathogen, and is usually susceptible to extended-spectrum cephalosporins [2]. Extended-spectrum β -lactamases (ESBLs) and plasmid-encoded AmpC enzymes are believed to be responsible for the resistance of *E. coli* isolates to extended-spectrum cephalosporins in hospital-acquired infections in Taiwan [3]. Of these isolates, CMY-2 is the most prevalent in Taiwan, and the prevalence is greater than the combined prevalence of the ESBL-producers CTX-M-3, CTX-M-14, and SHV-12 [3,4]. Other types of AmpC enzyme produced by *E. coli* include DHA-1, which has previously been identified in *Klebsiella pneumoniae* isolates in Taiwan [5]. However, AmpC enzymes are rarely seen in isolates acquired in the community or in the early period of hospital

admission. This report is of a patient with unanticipated CMY-2-producing *E. coli* septicemia, which occurred within 3 days of hospital admission after operation for traumatic intestinal perforations.

Case Report

A 43-year-old otherwise healthy woman underwent emergent laparotomy for acute abdomen by blunt abdominal trauma, which occurred in a traffic accident in 2006. At operation, multiple perforations of the small bowel and a laceration over the cecum resulting in fecal contamination of the peritoneal cavity were identified.

After surgery, amoxicillin-clavulanic acid 1.2 g every 6 h was administered intravenous (IV) because of the high risk for traumatic peritonitis. On day 3 of her hospital admission, she had a fever, up to 39°C, tachycardia, and hypotension. After obtaining blood for culture, antimicrobial therapy was changed to IV flomoxef 1 g every 6 h.

The blood culture yielded *E. coli*, which was resistant to amoxicillin-clavulanic acid, ceftriaxone, ceftazidime, and flomoxef, and susceptible to ceftazidime.

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ciprofloxacin, gentamicin, imipenem, and piperacillin-tazobactam by standard disk-diffusion test. The test for the ESBL phenotype was negative. Minimal inhibitory concentrations for the tested antibiotics were determined by the standard agar dilution method for cefotaxime (16 µg/mL), flomoxef (32 µg/mL), cefepime (0.25 µg/mL), ciprofloxacin (0.03 µg/mL), meropenem (<0.015 µg/mL), and colistin sulfate (2 µg/mL). The antimicrobial therapy was changed to IV ceftazidime 2 gm every 12 h plus metronidazole 500 mg every 8 h. However, the patient's condition worsened and she developed refractory septic shock and multiple organ dysfunction, including acute oliguric renal failure, persistent bacteremia, metabolic acidosis, severe thrombocytopenia, an elevated D-dimer of 1215 µg/L (normal range, <250 µg/L) and increased fibrin degradation products of 31 µg/mL (normal range, <5 µg/mL). Detailed laboratory data are shown in Table 1. The patient died on day 8, despite aggressive hemodynamic support and continuous veno-venous hemofiltration.

Using plasmid DNA of the isolated *E. coli* as templates, detection of the alleles of β-lactamase genes coding for the TEM, SHV, CTX-M, DHA, and CMY enzymes were performed by polymerase chain reaction amplification as described previously [4-8], using the following sets of primers: TEM-forward (5'-ATAAAT TCTTGAAGACGAAA-3') and TEM-reverse (5'-GACA GTTACCAATGCTTAATC-3') for partial *bla*_{TEM}; SHV-forward (5'-TGGTTATGCGTTATATCGCC-3') and SHV-reverse (5'-GGTTAGCGTTGCCAGTGC-3') for partial *bla*_{SHV}; CTX-M-14-forward (5'-AAAAATGA TTGAAAGGTGGTTGT-3') and CTX-M-14-reverse (5'-TTACAGCCCTTCGGCGATGA-3') for complete *bla*_{CTX-M-14}; CTX-M-3-forward (5'-TGTTGTTAGGA AGTGTGCCGC-3') and CTX-M-3-reverse (5'-TCGTT GGTGGTGCCATAG-3') for partial *bla*_{CTX-M-3}; DHA-1-forward (5'-CTGATGAAAAAATCGTTATC-3') and DHA-1-reverse (5'-ATTCCAGTGCCTCAAAAATA-3')

for complete *bla*_{DHA-1}; and CMY-2-forward (5'-CTGC TGCTGACAGCCTCTTT-3') and CMY-2-reverse (5'-TTTTCAAGAATGCGCCAGGC-3') for an internal fragment of approximately 95% of *bla*_{CMY-2}. Only amplicons for CMY-2 were observed. Furthermore, DNA sequencing analysis performed by an automated DNA sequencer (ABI PRISM 373; Applied Biosystems, Foster City, CA, USA) revealed 100% identity to the CMY-2 gene.

Discussion

Traumatic peritonitis, as a form of secondary peritonitis, may result in intra-abdominal abscesses, severe sepsis, and multi-organ failure [1,2]. Source control and appropriate antibiotics are the mainstays of treatment. For patients with community-acquired infections of mild-to-moderate severity, β-lactam/β-lactamase inhibitors such as ampicillin-sulbactam and amoxicillin-clavulanic acid are the preferred agents, as they act against aerobic Gram-negative organisms and anaerobic organisms [2]. Patients with more severe infections caused by *E. coli* or *K. pneumoniae* might benefit from an expanded-spectrum regimen, such as flomoxef or a third-generation cephalosporin (cefotaxime, ceftriaxone, or ceftizoxime). Regimens with antipseudomonal activity, including carbapenems, ceftazidime, cefepime, ciprofloxacin, and piperacillin-tazobactam are commonly recommended for nosocomial infections or pathogens with antibiotic-selective multiresistance [2]. However, the patient's clinical response, not the culture results, is the primary guide for directing changes in antimicrobial therapy [2,9].

Single-agent regimens have demonstrated benefits for patients with acute intra-abdominal infections [2,9]. However, no conclusive evidence suggests that 1 antibiotic regimen is better than any other for the

Table 1. Laboratory findings of a patient with *Escherichia coli* septicemia due to blunt abdominal trauma-associated peritonitis.

Parameter	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 8
White blood cells (/µL)	8100	4000	7200	3100	5300	5600	10,600
Band/segment (%)	0/55	35/52	42/50	45/40	37/44	20/71	22/68
Platelets (x 10 ³ /µL)	328	197	119	67	21	7	9
Blood urea nitrogen (mg/dL)	12	13	-	24	-	95	118
Creatinine (mg/dL)	0.9	0.9	-	1.4	-	4.5	5.0
C-reactive protein (mg/L)	-	-	-	-	190	-	-
Lactate (mmol/L)	8.8	4.7	5.8	6.6	-	3.3	3.9
Base excess ^a (mmol/L)	-8.0	-5.7	-6.1	-8.0	-6.7	-7.8	-10.6

^aAmount of acid needed to titrate 1 L of whole blood to the reference interval pH of 7.40.

first-line treatment of secondary peritonitis in adults. All regimens might show equivalent efficacy in terms of outcomes by either clinical or microbiological success, such as survival, time to defervescence, organ failure, duration of hospital stay, and prevention of intra-abdominal abscess and superinfection [2,9].

Due to the increasing resistance of *E. coli* in postoperative peritonitis to ampicillin-sulbactam or to amoxicillin-clavulanic acid, antimicrobial therapy should be tailored according to local susceptibility profiles [10]. A survey of 1034 bloodstream *E. coli* isolates from southern Taiwan during a 3.5-year period identified 30 isolates producing CMY-2, among which 26.7% were community-acquired [3]. Therefore, resistance of *E. coli* to flomoxef (third-generation cephamycin) or third-generation cephalosporins (cefotaxime, ceftriaxone, ceftizoxime, and ceftazidime) acquired in the community or during the early postoperative period (≤ 3 days), such as in this patient, remains rare.

AmpC enzymes, unlike ESBLs, are not inhibited by β -lactamase inhibitors and cephamycins, but are commonly susceptible to fourth-generation cephalosporins (cefepime and ceftipime) and carbapenems [11,12]. The presence of the CMY-2 AmpC enzyme in *E. coli* may partially explain the worsening septicemia of this patient despite initial amoxicillin-clavulanate and subsequent flomoxef therapy. The independent risk factors for bacteremia caused by CMY-2-producing *E. coli* include nosocomial infections with prior use of a β -lactamase inhibitor and an extended-spectrum cephalosporin [3]. However, it is difficult to discern whether the CMY-2 production in *E. coli* in this patient was associated with the use of amoxicillin-clavulanate for such a short duration of < 3 days.

In conclusion, this report suggests that continuous monitoring for CMY-2 or other AmpC enzymes in the organisms isolated from patients with traumatic peritonitis caused by blunt abdominal trauma is necessary. Furthermore, further investigation is needed into whether selection of an anti-AmpC regimen such as ceftipime, cefepime, or a carbapenem is appropriate as first-line treatment, particularly for more severe infections.

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