CASE REPORT

Intraabdominal Infection Caused by Extremely Drug-Resistant *Klebsiella pneumoniae* Successfully Treated with Ceftazidime/Avibactam in Combination with Aztreonam: The First Case Report in Thailand

Woraphot Tantisiriwat, MD, MPH[1], Suchat Jerajakwatana, MD[1], Thawat Mongkolporn, MD[1], Varayu Prachayakul, MD[1], Thongchai Leelayuthachai, MD[2], Hiran Phiphitthanaban, MD[2], Jutamas Dechsanga, MD[2], Tachapol Virunhagarun, MD[1], Chartchai Suntiparpluacha, MD[1], Manee Suwansirikul, MD[3], Usanee Sermdamrongsak, MD[4], Chingyiam Panjapiyakul, MD[5]

[1] Department of Medicine, Samitivej Sukhumvit Hospital, Bangkok, Thailand; [2] Intensive Care Unit, Samitivej Sukhumvit Hospital, Bangkok, Thailand; [3] Department of Rehabilitation Medicine, Samitivej Sukhumvit Hospital, Bangkok, Thailand; [4] Department of Anesthesiology, Samitivej Sukhumvit Hospital, Bangkok, Thailand; [5] Department of Surgery, Samitivej Sukhumvit Hospital, Bangkok, Thailand

A 54-year-old Bangladesh female was referred to a Thai private hospital for management of her serious illness. She was found to have intraabdominal infection from perforation at the second part of the duodenum and the right sided empyema. The initial pleural fluid culture from Bangladesh grew *Klebsiella pneumoniae*, which was susceptible only to tigecycline. She underwent laparoscopy and drainage of intraabdominal collection with two intraabdominal and bilateral intercostal drainage catheters. She also underwent endoscopic retrograde cholangiopancreatography (ERCP) for insertion of common bile duct cover stenting over the perforation site. Again, the culture from the collection grew pandrug-resistant *K. pneumoniae*. She was successfully treated with a 10-day course of ceftazidime/avibactam in combination with aztreonam from Bangladesh. At least two subsequent cultures from abdominal drainage tubes after completion of ceftazidime/avibactam in combination with aztreonam did not show pandrug-resistant *K. pneumoniae* anymore. All the left over small intraabdominal collections were resolved at three months follow up after hospital discharge without any further antibiotic treatment.

Keywords: Extremely drug resistance; *Klebsiella pneumoniae*; Ceftazidime/avibactam; Aztreonam; Thailand

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Carbapenem-resistant Enterobacterales (CRE) are currently among the worldwide antimicrobial resistance threats[1]. Carbapenemase production is the most common mechanism among these CRE isolates. In South Asia and South-East Asia, the concerning carbapenemases are the New Delhi metallo-β-lactamases (NDMs) more than oxacillinases (OXA) and *Klebsiella pneumoniae* carbapenemases (KPC)[2,3]. In Thailand, NDMs following by OXA-48 like carbapenemases are frequently observed among CRE clinical isolates[2]. The NDM-1-producing CRE infection cases were first reported in 2014[4].

The current recommendation for the treatment of the NDM-producing CRE by the Infectious Diseases Society of America is the combination of ceftazidime/avibactam and aztreonam or cefiderocol monotherapy[1]. Both aztreonam and cefiderocol are not currently available in Thailand. The current available options for the treatment of NDMs CRE infection in Thailand include tigecycline, fosfomycin, aminoglycosides or colistin alone or in combination with or without carbapenems, depending on an in vitro susceptibility test result.

The authors recently encountered a Bangladesh patient with intraabdominal infection caused by extremely drug-resistant *K. pneumoniae*. Regarding in-vitro susceptibility result, there were no current available antibiotics for the treatment option.

Correspondence to:

Panjapiyakul C.
Samitivej Sukhumvit Hospital, Bangkok 10110, Thailand.
Phone: +66-2-7118000
Email: chingyiam@yahoo.com

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Case Report

A 54-year-old Bangladesh female was referred from her country to a Thai private hospital for further management of her serious illness. Upon arrival, she

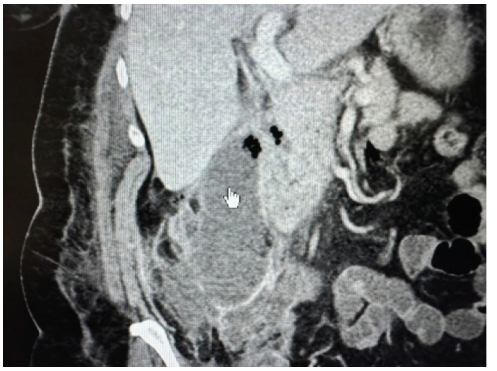

Figure 1. Initial CT scan of the abdomen (13.2×4.2×4.7 cm para-duodenal retroperitoneal fluid collection).

had a fever of 38.1 degree Celsius and was intubated on a mechanical ventilator. The initial computerized tomography (CT) scan of chest and abdomen revealed bilateral pleural effusions, free-air around duodenum and a 13.2×4.2×4.7 centimeter (cm) para-duodenal retroperitoneal fluid collection (Figure 1). Her initial blood test showed leukocytosis with left shift, complete blood count (CBC) exhibited white blood cell (WBC) of 25,750 cells/mm^3, neutrophil (N) 88%. The right pleural fluid culture from Bangladesh grew carbapenem-resistant *K. pneumoniae* (CRK), which was susceptible only to tigecycline as it had resistance to colistin. She had received tigecycline and imipenem from Bangladesh, which were adjusted to tigecycline and biapenem. She also had the right internal jugular (IJ) central line insertion.

Magnetic resonance imaging of upper abdomen and magnetic resonance cholangiopancreatography showed a probably concealed second part duodenal perforation, an 8.5×8.0×13.8 cm lobulated fluid collection with partial wall-off, at right anterior pararenal and perirenal spaces with extraperitoneal extension, mild focal interstitial edematous pancreatitis at head, and uncinate process and reactive inflammation of second part of duodenum.

Two days after hospitalization, she underwent laparoscopic drainage of intraabdominal abscess with two silicone tubes, number 24 French unit, and bilateral intercostal drainage (ICD) tubes was also performed. Pus from intra-abdominal abscess Gram stain showed Gram-negative bacilli and subsequently grew CRK, which was only susceptible to tigecycline with minimal inhibitory concentration (MIC) of 2 µg/mL and *Citrobacter korseri*, which was susceptible to biapenem. Tigecycline dosage had then increased to 100 mg every 12 hours. The right pleural fluid WBC was 24,240 cells/mm^3 with N 79%, subsequent culture was no growth, while the left pleural effusion fluid WBC was 10 and subsequent culture was no growth.

She gradually improved and continued to be afebrile. Her CBC had improved with WBC decreased to 9,930 cells/mm^3 and N 73%. Eight days after hospitalization, she developed a new fever of 38.7 degree Celsius. Two blood cultures were obtained, and micafungin was initiated for possible *Candida* infection. Her CBC showed WBC of 14,100 cells/mm^3 and N 71%. The new CT scan of her abdomen showed decreased size of rim-enhancing fluid collection to about 6.1×2.8×2.9 cm. The left ICD was removed. The CBC still showed leukocytosis with WBC of 14,860 cells/mm^3 and N 80%. The pus from abdominal drainages were sent for culture.

Again, the pus culture grew CRK, which was resistant to tigecycline and all other antibiotics but only intermediate to colistin. Antibiotics were adjusted to colistin and co-trimoxazole and again the pus culture from abdominal drainages was sent for culture. She underwent endoscopic retrograde cholangiopancreatography (ERCP) to insert the common bile duct (CBD) cover stenting for prevention of further leakage from the perforation site.

The authors had discussed with her husband the option of antibiotic treatment for the patient. Ceftazidime/avibactam in combination with aztreonam was the best option for this situation but aztreonam was not available in Thailand. Her husband decided to bring aztreonam from Bangladesh. The subsequent additional susceptibility test for co-trimoxazole showed resistant result, so co-trimoxazole was discontinued.

The patient had low grade temperature of 37.6 degree Celsius. CBC showed WBC of 15,010 cells/mm^3 and N 77%. The antibiotics were adjusted to colistin and ceftazidime/avibactam in combination with aztreonam. Ceftazidime/avibactam 2.5 gram was given every eight hours intravenously along with aztreonam 2 gram every eight hours and finished at the same time on the sixteenth day of hospitalization. Both antibiotics were given by prolonged infusion around three hours starting from the second dosage.

Pus from the abdominal drainage before these antibiotics' adjustment later grew pandrug-resistant *K. pneumoniae* (Figure 2). Colistin was discontinued, the authors also used daily suction of both abdominal drainage tubes to enhance clearing of the intraabdominal pus (Figure 3).

After 17 days of hospitalization, she gradually

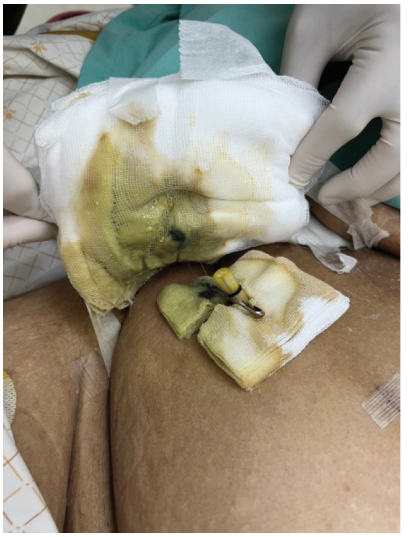

Figure 2. Pus from the abdominal drainage before ceftazidime/avibactam in combination with aztreonam.

Figure 3. Daily suction to both abdominal drainage tubes.

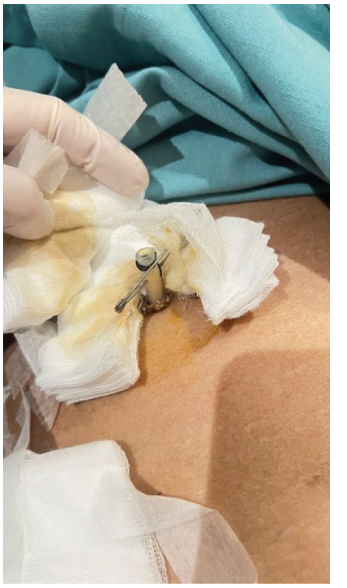

Figure 4. Pus from the abdominal drainage after 10-day course of ceftazidime/avibactam in combination with aztreonam.

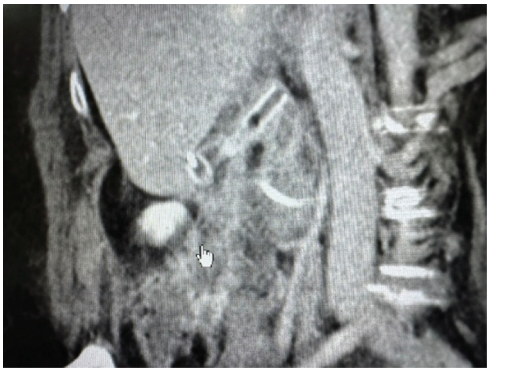

Figure 5. CT scan of the abdomen after ceftazidime/avibactam in combination with aztreonam (decreased in size of rim-enhancing fluid collections).

improved, became afebrile and was extubated. CBC showed WBC decreased to 12,970 cells/mm³ with N 93%. Liver function tests (LFT), after four days of ceftazidime/avibactam in combination with aztreonam, revealed increasing value of alanine transaminase (ALT) enzyme from 131 to 387 unit per liter (U/L) and alkaline phosphatase (ALP) from 333 to 817 U/L without any symptoms.

Pus from abdominal drainage seemed to be clearer and was cultured repeatedly (Figure 4). Followed up (F/U) CT scan of the abdomen showed slightly decreased in size of now two rim-enhancing fluid collections, one at right supra-renal region about 2.9×1.8×3.5 cm and another at right anterior pararenal space and right retroperitoneal region about 4.1×3.6×5.8 cm (Figure 5).

After 26 days of hospitalization, the patient had an episode of fever 38.9 degree Celsius. Hemoculture from peripheral vein and central line were checked. Vancomycin was given concerning possible central line infection. CBC revealed WBC of 12,110 cells/mm³ and N 82%. The right ICD was removed. The pus from abdominal drain culture grew *Staphylococcus hemolyticus* and *Candida tropicalis*, while blood cultures were no growth. Micafungin was added to vancomycin. Ceftazidime/avibactam and aztreonam

were discontinued. She became afebrile with clinical improvement. F/U LFT revealed decrease ALT to 76 U/L, 38 U/L and ALP to 327 U/L, 189 U/L (at four and ten days after discontinuation of ceftazidime/avibactam and aztreonam, respectively).

After 30 days of hospitalization, F/U CBC revealed WBC of 8,710 cells/mm³ and N 72%. Four days later, the patient had a febrile episode of 39 degree Celsius. F/U pus culture grew carbapenem-resistant *Acinetobacter baumanii* (CRAB), which was intermediate susceptibility to colistin with a MIC of less than 0.5 µg/mL, sensitive to sitafloxacin and sensitive to tigecycline with a MIC of 4 µg/mL. Antibiotics were adjusted to colistin, sitafloxacin, and sulbactam. Micafungin and vancomycin were discontinued. Right IJ central line was removed.

After 40 days of hospitalization, F/U CT scan of chest and abdomen revealed decrease in size of two rim enhancing fluid collections to about 2.4×1.5×1.8 cm and 2.1×1.1×5 cm, respectively and a questionable thrombosis at right supraclavicular area. The drainage tube from the right supra-renal region was removed. Ultrasound of the neck revealed a thin eccentric fibrotic band at the distal right IJ vein to the visualized proximal part of the right subclavian vein, sequelae of thrombosis with near complete recanalization.

Subsequent pus culture revealed pandrug-resistant *K. pneumoniae* and CRAB while the tip of drainage catheter only grew *K. pneumoniae*, which was only sensitive to tigecycline. Both pandrug-resistant *K. pneumoniae* and CRAB were considered to be abdominal drainage tube colonization. All antibiotics were discontinued. She was afebrile and had stable vital signs one day prior to antibiotic discontinuation. CBC revealed WBC of 9,640 cells/mm³ and N 69%.

After 49 days of hospitalization, the patient was afebrile. F/U CBC revealed WBC 8,870 cells/mm³ and N 68%, ALT 66 U/L, and ALP 179 U/L. Pus culture from the abdominal drain grew *K. pneumoniae*, which was sensitive only to tigecycline. She was discharged on the fiftieth day of hospitalization and F/U as outpatient for wound care.

Nine days after discharge, F/U CT scan of abdomen showed no fluid collection at the same level of previous figures (Figure 6) but still decreased in size of left over rim enhancing fluid collections to around 1.7×0.7 cm at posterior to the previous shown level, 1.7×2.8 cm at right anterior pararenal space abutting psoas muscle (Figure 7) and 2.5×1.7 cm at posterolateral aspect of the right anterior pararenal space. Three days later, the abdominal drainage tube was removed.

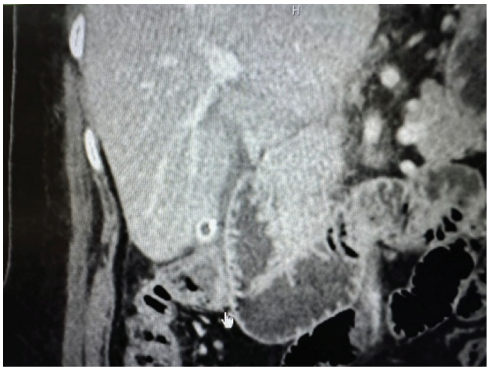

Figure 6. CT scan of the abdomen before the last drainage tube removal (no fluid collection at the same level as of Figure 1 and 5).

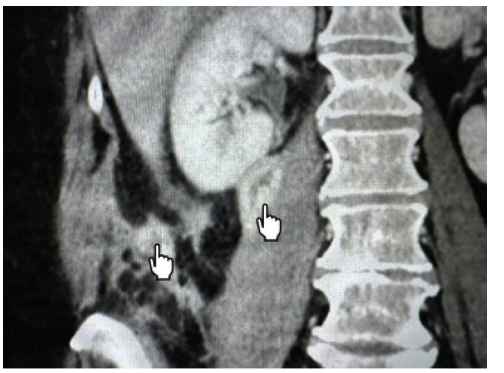

Figure 7. CT scan of the abdomen before the last drainage tube removal (decrease in size of rim enhancing fluid collections to around 1 cm at posterior to previous level and 1×2 cm at psoas muscle).

Fifteen days after hospital discharge, she was afebrile and had stable vital signs. F/U CBC revealed WBC of 6,910 cells/mm³ and N 64%, ALT 60 U/L, and ALP 161 U/L. Both pus culture from drainage tube and tip of drainage tube grew CRAB, which were considered to be drainage tube colonization.

Twenty-one days after hospital discharge, F/U CBC revealed WBC of 8,530 cells/mm³ and N63%, ALT 55 U/L, and ALP 155 U/L. She was well without a fever and symptoms. She returned to her country a few days later without any further antibiotic treatment.

Ninety-four days after hospital discharge, she had returned for F/U. F/U CT scan of abdomen showed no left-over fluid collections, without any further antibiotic treatment since discharge (Figure 8).

She was informed and consented to have her medical record reviewed and data published.

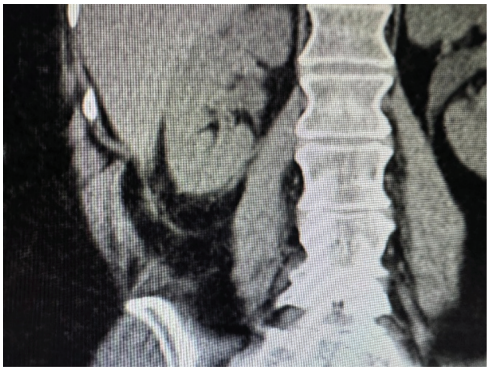

Figure 8. CT scan of the abdomen at F/U visit on the 94th date after hospital discharge (no left-over fluid collections detected).

Discussion

According to surviving sepsis campaign, the International Guidelines for Management of Sepsis and Septic Shock 2021, the management for the present case should be focused on source control and appropriate antibiotic management[5]. The source control included either laparoscopic or opened adequate drainage of the intraabdominal pus collection with two silicone drainages placement. The patient also had ERCP with CBD cover stenting to prevent further leakage from perforation site. The drainage tubes were suctioned daily until no further pus drained.

Many publications described the epidemiology of carbapenemases in Bangladesh[3,6-9]. Metallo-β-lactamases type of the carbapenemases were the predominant gene. According to the most recent specific data from Bangladesh, Farzana et al. reported that the gene bla_{NDM} was predominated for around 85% followed by $bla_{OXA-181}$ around 12.4%[3].

For the appropriate antibiotic management, the critical issue was the situation when the authors discovered CRK that was resistant to all available antibiotics. Two recent case reports and a case series revealed the successful results of suspected NDM CRK treated with ceftazidime/avibactam in combination with aztreonam[10-12].

The current data suggested that ceftazidime/avibactam in combination with aztreonam should be active against 90% of metallo-β-lactamases producing Enterobacterales isolates[13-18]. In light of these information, the authors considered treating the patient with ceftazidime/avibactam in combination with aztreonam even though the susceptibility data of this CRK to ceftazidime/avibactam in combination with aztreonam was not available.

The administration of ceftazidime/avibactam and aztreonam in the present case was highlighted for both antibiotics to be infused and finished at the same time. The reason for this action was to protect aztreonam. Although aztreonam is not hydrolyzed by the NDMs, it can be hydrolyzed by other beta-lactamase enzymes such as OXA or extended spectrum beta-lactamase enzymes[1], which could co-exist in this organism[3,11]. Avibactam would protect aztreonam from this possible hydrolyzation[1].

Both antibiotics were administered via prolonged 3-hour infusion, after the initial loading dose, to optimize pharmacodynamic parameters for bacterial eradication. This approach aligns with evidence from a systematic review and meta-analysis by Vardakas et al. demonstrating mortality reduction with prolonged β-lactam infusions versus intermittent bolus administration[19].

Vigilant LFT monitoring is essential during ceftazidime/avibactam and aztreonam therapy. Clinical data from Lodise et al.[20], revealed 40% (19/47) incidence of ALT/AST elevation. There were treatment discontinuations due to severe transaminitis in two cases. All cases were asymptomatic without hepatic synthetic dysfunction and had complete resolution post-therapy cessation.

Formulary inclusion of aztreonam is expected to be available in Thailand within the year 2025. This expansion becomes critical given the setting of limited antibiotic option for suspected serious NDM CRK infection.

The present case report had limitations as it is from a single patient, which limits the ability to generalize the findings to a larger population. The microbiological analysis lacked advanced molecular diagnostics that could provide detail insights into resistance mechanisms. The pharmacokinetic and pharmacodynamic data were not available to optimize the dosing and duration of antibiotic therapy. Some antibiotics used in the treatment were not locally available. Therefore, this may restrict the applicability of this approach in similar resource-limited settings, and the follow-up period was short, limiting assessment of long-term outcomes and relapse.

Conclusion

Ceftazidime/avibactam in combination with aztreonam for ten days successfully cleared the extremely drug-resistant CRK intra-abdominal infection with two proven subsequent culture results and clearing of the abscesses at three months F/U after hospital discharge without any further antibiotic treatment.

What is already known about this topic?

One option by the current international recommendation for treatment of the NDMs CRK is the combination of ceftazidime/avibactam and aztreonam.

What does this study add?

Therapy with ceftazidime/avibactam in combination with aztreonam should be available in Thailand soon.

The administration of ceftazidime/avibactam in combination with aztreonam should be at the same time and preferable for prolonged intravenous drip.

Elevation of ALT and ALP values are common adverse effects that improve after discontinuation of ceftazidime/avibactam and aztreonam.

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Conflicts of interest

The authors declare no conflicts of interest.

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