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CASE REPORT

Antagonistic effect between tigecycline and meropenem: successful management of KPC-producing *Klebsiella pneumoniae* infection

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Abstract

Introduction A woman infected by carbapenem-resistant *Klebsiella pneumoniae* is reported in this study.

Case report Tigecycline and meropenem combination was used, and indeed, in vitro checkerboard synergy test confirmed the antagonism between the two antibiotics. Thus, meropenem was ceased and single high-dose tigecycline was successful against the infection. Subsequent experiments showed that the isolates of the KPC-2-producing *K. pneumoniae* ST11 clone caused the infection.

Conclusion Therefore, tigecycline and meropenem combination should be used with caution.

Keywords Carbapenem-resistance · KPC-2-producing *Klebsiella pneumoniae* · Tigecycline · Meropenem · Antagonistic effect

Introduction

Carbapenemase-producing *Klebsiella pneumoniae* has emerged as a global major public health problem for its rapid dissemination and resistance to multiple antibiotics, especially carbapenems [1–4]. In China, KPC-2 is the most represented carbapenemase among carbapenem-resistant *K. pneumoniae* isolates detected in tertiary hospitals [1, 5]. Since the optimal treatment remains elusive [2], one Chinese consensus statement regarding extensively drug-resistant Gram-negative infections suggests to consider the option of a combination treatment between tigecycline and carbapenem [6]. Here, we present a clinical case study involving a woman affected by sepsis, pneumonia and bacteriuria caused by KPC-2-producing *K. pneumoniae*, which confirmed the antagonistic effect between tigecycline and meropenem in vitro.

A 43-year-old woman, who lost consciousness after sudden convulsion, was subsequently admitted to our hospital

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in November 2017. The patient underwent surgical abortion procedure 6 days earlier, subsequently developing a fever higher than 39 °C, upper abdominal pain, nausea, and vomiting. The blood test showed elevated amylase, while abdominal CT scan showed acute cholecystitis and peripancreatic exudation. The patient was treated with cefotaxime and metronidazole to combat infection and somatostatin for suspected pancreatitis.

The patient was immediately transferred to the emergency department of our hospital after loss of consciousness and no detectable blood pressure. She gradually regained consciousness after a quick rehydration, with a peak temperature of 38.5 °C. Blood test results were as follows: leucocyte 15.1×10^9/L, neutrophils 12×10^9/L, C-reactive protein (CRP) 82.3 mg/L, procalcitonin 0.47 ng/mL, liver, kidney and heart function injury, and coagulation disorders. Enhanced CT scan showed peripancreatic exudation, gallbladder fossa effusion, and ascites. A temporary pacemaker was implanted for a III-degree atrioventricular block. An empirical antibiotic therapy was started and the patient was intravenously (i.v.) treated with piperacillin/tazobactam 4.5 g every 8 h, but the peak temperature remained above 38 °C every day.

On day 4 of hospitalization, the patient was transferred to the cardiology department and she soon displayed shortness of breath, cyanosis, mental haziness, and blood pressure reduction. CRP was 84.78 mg/L and procalcitonin was 2.62 ng/mL. Septic shock caused by abdominal infection was suspected, and the patient was transferred to the intensive care unit on day 5. Subsequently, tracheal intubation, mechanical ventilation, and continuous renal replacement therapy were performed. Piperacillin/tazobactam was replaced with an i.v. administration of meropenem 0.5 g every 8 h against the infection. On day 8, ascites from abdominal cavity by puncture and the sputum were collected. On day 10, the presence of *K. pneumoniae* was reported in the sputum, and it was resistant to imipenem and meropenem (MIC = 16 μg/mL, microdilution method) and piperacillin/tazobactam (MIC > 128 μg/mL, microdilution method), and sensitive only to tigecycline (MIC = 0.5 μg/ml, *E* test method). No bacteria were found in the ascites from abdominal cavity. A potential bacterial colonization could not be excluded because of the presence of bacteria in the sputum. The body temperature dropped to 37.8 °C and CRP was 30 mg/L, and then, extubation was performed and meropenem was stopped.

On day 13, the fever rose again to more than 39 °C, and CRP was 28.05 mg/L, while procalcitonin was 0.38 ng/mL. Blood and urine samples were collected and piperacillin/tazobactam 4.5 g i.v. every 8 h was administered again. Except for fever, the patient's overall conditions improved, continuous renal replacement therapy was ceased and the temporary pacemaker was removed. She was transferred again to the cardiology Department on day 14, with blood and urine culture resulting positive for carbapenem-resistant *K. pneumoniae*. CRP was 41.17 mg/L, procalcitonin was 0.46 ng/mL, and urinalysis showed pyuria and positive leukocyte esterase. Thus, the antibiotic regimen was changed to meropenem 2 g every 8 h plus tigecycline 100 mg every 12 h, both i.v., after consultation with the infectious disease specialists, and furacilin was administered for washing the bladder. It was not possible to choose colistin, because it had not entered the Chinese market at that time. Despite the 2 days administration of meropenem and tigecycline combination, the body temperature remained at 38 °C, CRP value remained at 35.5 mg/L, and procalcitonin level was 1.1 ng/mL.

Since the combination of tigecycline and meropenem was used, the in vitro antibiotic synergy test was performed by checkerboard method (Fig. 1a). Fractional inhibitory concentration indices ($\sum_{FIC}$) of tigecycline and meropenem were calculated, and according to the interpretation of checkerboard synergy testing, $\sum_{FIC} > 4$ indicated an antagonistic behavior [7]. MIC of tigecycline alone was 1 μg/ml, while MIC of meropenem alone was 16 μg/mL (Fig. 1a). When the concentration of tigecycline was 0.5 μg/mL, the concentration of combined meropenem needed to reach 128 μg/mL to inhibit bacterial growth, which confirmed the antagonistic effect between tigecycline and meropenem with $\sum_{FIC} = 8.5$.

As the antagonism in vitro was confirmed, meropenem was stopped, while i.v. administration of tigecycline 100 mg every 12 h continued as an anti-infective therapy on day 17. By day, 18 CRP remained at 37.0 mg/L. On day, 19 CRP dropped to 21.9 mg/L and the temperature was normal. Pulsed field gel electrophoresis (PFGE) of conserved XbaI fragments of the three collected *K. pneumoniae* isolates from the sputum, blood, and urine was performed as previously described [5], as shown in Online Resource 1. This test showed that the three isolates were highly homologous, and the possibility that the same bacterium from the respiratory tract caused the secondary infection in blood and urine was strongly suspected. The bla_{KPC} gene and bla_{NDM} gene were confirmed by PCR and sequencing, and the sequence alignments confirmed that only bla_{KPC-2} gene was positive for the isolates [5]. Multilocus sequence typing (MLST) confirmed that the only dominant clone was ST11 [5]. The source of the KPC-producing *K. pneumoniae* could not be determined for the lack of evidence. It might be a nosocomial infection due to the abortion procedure, or from the environment of the intensive care unit [8, 9]. By day 30, tigecycline was stopped. The patient finally recovered and was discharged on day 36. From the moment, the patient was discharged until the time when this report was written, more than 6 months have passed, in which the patient has perfectly recovered, without showing signs of bacterial infection anymore.

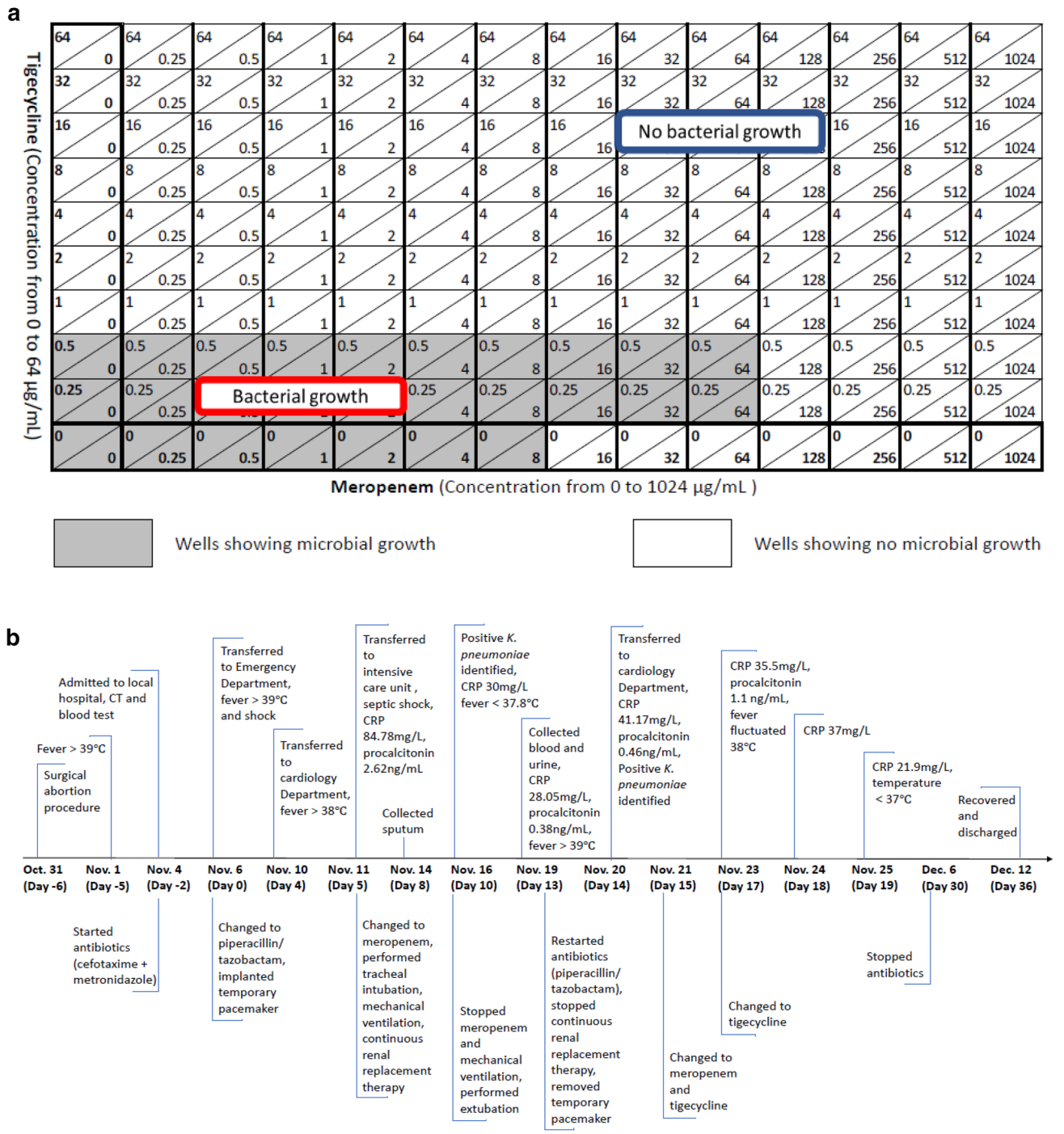

Fig. 1 In vitro checkerboard synergy test results and a clinical timeline. **a** Diagram of the 96 wells checkerboard plate is shown. In each well, the number written above indicated the tigecycline concentration, while the number written below indicated the meropenem concentration. The dark wells indicated bacterial growth visible to the naked eye, while the white wells indicated no bacterial growth after 16–20 h incubation at 37 °C. **b** Timeline of the patient's clinical course

Combination of tigecycline and other antibiotics is recommended for carbapenem-resistant *K. pneumoniae* infection [2, 6], but in former KPC-producing *K. pneumoniae*-infected animal models, the combination of tigecycline and meropenem was not showing any synergistic effect in vivo [10–12] and in vitro [11, 13]. In this case, the in vitro checkerboard test was repeated, the antagonistic effect between tigecycline and meropenem, when combined, was confirmed, but the reason why it caused the patient's poor treatment response remains still unclear. One reasonable explanation might be

that tigecycline is bacteriostatic and meropenem is bactericidal. Tigecycline could interrupt the KPC-producing *K. pneumoniae* isolate to uptake or import meropenem, which resulted in an antagonistic effect [14–16]. However, the association between in vitro antagonistic effect and in vivo ineffective outcome needs to be confirmed among more clinical *K. pneumoniae* isolates and clinical cases.

In summary, in this study, tigecycline and meropenem combination appeared to be antagonistic in vitro against KPC-producing *K. pneumoniae* isolates, which was not mentioned in the Chinese anti-extensively drug-resistant Gram-negative bacilli infection consensus statement [6]. Although a single clinical experience is described in this report, we are revealing that the antagonism between tigecycline and meropenem should not be underestimated and tigecycline and meropenem combination against KPC-producing *K. pneumoniae* infections should be used with caution.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This is a research involving a human participant.

Informed consent The patient provided written informed consent to publish the clinical record.

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