

Persistent Klebsiella septicemia

Saturday, 01 October 2005

A 15-year-old girl was admitted to the hospital because of mild abdominal pain and fever up to 37.8°C of 2-day duration. Specifically, she developed peri-umbilical abdominal pain that gradually moved to the right lower abdominal quadrant. In addition, she vomited twice on the day of admission. Her past medical history was unremarkable. She was not receiving any medications.

Physical examination on admission showed temperature 38°C, respiratory rate 14 breathes/min, arterial blood pressure 120/70 mm/Hg, and heart rate 84 beats/min. There was mild tenderness during the palpation of the right lower abdominal quadrant. There was no rebound tenderness or abdominal wall rigidity. The rest of the examination was normal.

Routine laboratory testing on admission revealed increased leucocytes (12,360 white blood cells per mm³ of peripheral blood, 86.3% neutrophils). Liver function tests and serum creatinine, urea, electrolytes, and glucose were normal. An abdominal ultrasound showed small amount of fluid in the Douglas pouch.

The patient received intravenous metronidazole 500 mg every 8 hours and tazobactam/piperacillin 4/0.25 gr every 8 hours after her admission to the hospital. Appendicitis was considered as the most likely diagnosis. The patient underwent laparoscopic appendectomy 40 hours after her admission. No transfusion of blood products was needed. The intra-operative findings were consistent with inflammation of the appendix (erythema and edema). In addition, a small amount of cloudy fluid was seen in the Douglas pouch.

Despite the operation, the patient continued to have fever and rigors. In fact, a gradual increase of the body temperature was noted during the post-operative period. There was no evidence from the physical examination and the laboratory and imaging testing for any of the likely causes of post-operative fever such as respiratory or urinary tract infection, post-operative wound infection, atelectasis, deep venous thrombosis, and drug fever.

Klebsiella pneumoniae was isolated from cultures of blood specimens, which were taken for first time during the second post-operative day. The pathogen was resistant to 1st, 2nd, and 3rd generation cephalosporins, quinolones, piperacillin/tazobactam, and aztreonam, intermediately susceptible to meropenem (mean inhibitory concentration, MIC = 8 mg/l), and susceptible to gentamicin and colistin. Cultures of urine specimens did not grow any micro-organisms. Chest and abdominal x-rays, abdominal ultrasound, as well as computed tomography (CT) scan of the chest and upper and lower abdomen, a transthoracic echocardiogram, ultrasound triplex testing of the intra-abdominal arteries and veins as well the lower extremities veins, and a gallium nuclear medicine scan did not reveal any abnormal findings.

The patient continued to have high fever (up to 39.8 °C), sweating, malaise, and persistent isolation of Klebsiella pneumoniae from blood specimens, despite the administration of various antimicrobial regimens, including the use of intermittent intravenous gentamicin (60 mg every 8 hours), meropenem (1g every 8 hours), and colistin (1.000.000 units every 8 hours).

What are the therapeutic options?

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Discussion

Her symptoms improved only 36 hours after the initiation of the treatment with continuous intravenous administration of 6 g/day of meropenem and subcutaneous low molecular weight heparin (60 mg enoxaparin twice a day) (Figure 1. Diagram of the maximum and the mean daily temperature during the 27-day hospitalization of the patient. The doubling of the daily intravenous dose of meropenem (2 g every 8 hours from 1 g every 8 hours) was done during the 9th day of hospitalization and was followed by transient reduction of the fever. The patient became afebrile and the persistent *Klebsiella pneumoniae* bacteremia resolved after the administration of continuous intravenous meropenem during the 17th day of hospitalization). She received this treatment for 10 days and then she was discharged from the hospital without any symptoms. She was completely asymptomatic during a 3-month of regular follow up.

The most noteworthy point of our case report is the fact that the persistent *Klebsiella pneumoniae* septicemia was cured only with the continuous intravenous administration of meropenem. It is interesting that septicemia persisted despite various antimicrobial regimens for about twelve days. It should be mentioned that the patient had a transient reduction of the temperature when the dosage of intravenous meropenem was doubled (2 g every 8 hours from 1 g every 8 hours). Of note, the isolate of *Klebsiella pneumoniae* had intermediate susceptibility to meropenem, and thus, the total daily dose and the mode of the administration of the antibiotic (continuous versus intermittent intravenous administration) was likely to have a considerable impact on the effectiveness of the antibiotic.

We recently published a meta-analysis of randomized control trials comparing the continuous with the intermittent intravenous administration of antimicrobial agents (1). The evidence from the analyzed trials supports that the continuous intravenous administration of antibiotics (especially beta-lactams) should be considered in patients with serious infections with bacteria that have high minimal inhibitory concentration (MIC) for the administered antimicrobial agents. In addition, we performed a systematic review of randomized controlled trials in order to examine pharmacokinetic and pharmacodynamic aspects of the comparison of continuous with the intermittent intravenous administration of antimicrobial agents (2). The study showed that the continuous intravenous infusion of antibiotics with time-dependent bacterial killing (such as beta-lactams) seems to be superior compared to the intermittent intravenous administration, from a pharmacodynamic point of view, at least when confronting bacteria with high MICs for the studied antibiotics. In this case report, we present our experience with a patient who had persistent *Klebsiella pneumoniae* septicemia that was cured only after continuous intravenous administration of meropenem.

Although we could not identify the specific source of the septicemia, we believe that the infection had an intra-abdominal origin (appendicitis) with seeding of the pathogen into an intra-vascular focus and thus, continuation of the infection. It is interesting that the increased intra-abdominal pressure during laparoscopic surgery may promote the translocation of bacteria from the intra- abdominal focus of the infection to the blood (3;4). Although an intra-vascular focus of the persistent *Klebsiella pneumoniae* septicemia was not documented with the imaging tests, it should be emphasized that even modern imaging tests such as computed tomography (CT) scan and ultrasound testing of the vessels may miss an area of septic thrombophlebitis. For example, in a study by Brown et al. only 54 out of 69 women with enigmatic postpartum fever, that were postulated to have septic pelvic thrombophlebitis, had documentation of this diagnosis by the imaging tests (5).

It is not clear whether *Klebsiella pneumoniae* was part of the intra-abdominal infection from the beginning or whether it was a nosocomially-acquired pathogen. The fact that the pathogen was a multidrug resistant strain favors the second possibility. However, it should be noted that the pathogen was first isolated from a blood culture specimen taken during the third hospital day, a fact that may suggest another explanation, i.e. *Klebsiella pneumoniae* could have been part of

the initial abdominal infection and could have acquired a gradually resistant antimicrobial profile due to the administered antimicrobial treatment.

We must acknowledge that another therapeutic intervention besides the continuous intravenous administration of meropenem was done to our patient before she became afebrile, namely the subcutaneous administration of low molecular heparin. However, the effectiveness of heparin for the treatment of patients with septic thrombophlebitis in various body sites is controversial. This is because of the relatively scarcity of evidence on this issue. There are several case reports that present controversial experience regarding the effectiveness of heparin in patients with septic thrombophlebitis (6;7). There is only one randomised controlled trial performed on 69 patients with postpartum fever that failed to show that heparin treatment is effective in this population (5).

In conclusion, our young patient with persistent post-appendectomy *Klebsiella pneumoniae* septicemia was cured only after the continuous intravenous administration of meropenem. Our case offers additional support to the use of this mode of administration of antimicrobial agents in patients with severe infections with bacteria that have relatively high minimal inhibitory concentration (MIC) for the administered drugs. This treatment option may be considered early in the treatment of patients with serious infections, especially when antibiotics with time-dependent action are used such as beta-lactams.

Acknowledgement

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Reference List

1. Kasiakou SK, Sermaides GJ, Michalopoulos A, Soteriades ES, Falagas ME. Continuous versus intermittent intravenous administration of antibiotics: a meta-analysis of randomised controlled trials. *Lancet Infect.Dis.* 2005;5(9):581-9.
2. Kasiakou SK, Lawrence KR, Choulis N, Falagas ME. Continuous versus intermittent intravenous administration of antibiotics with time-dependent anti-bacterial action: A systematic review of pharmacokinetic and pharmacodynamic parameters. (in press). *Drugs* 2005.
3. Ozmen MM, Col C, Aksoy AM, Tekeli FA, Berberoglu M. Effect of CO(2) insufflation on bacteremia and bacterial translocation in an animal model of peritonitis. *Surg.Endosc.* 1999;13(8):801-3.
4. Evasovich MR, Clark TC, Horattas MC, Holda S, Treen L. Does pneumoperitoneum during laparoscopy increase bacterial translocation? *Surg.Endosc.* 1996;10(12):1176-9.
5. Brown CE, Stettler RW, Twickler D, Cunningham FG. Puerperal septic pelvic thrombophlebitis: incidence and response to heparin therapy. *Am.J.Obstet.Gynecol.* 1999;181(1):143-8.
6. El Braks R, Harnois F, Boutros N, Fallik D, Roudie J, Smadja C et al. Mesenteric adenitis and portal vein thrombosis due to *Fusobacterium nucleatum*. *Eur.J.Gastroenterol.Hepatol.* 2004;16(10):1063-6.
7. Vogel RA, Hall CI, Viney RS. Septic pylephlebitis following shigella bacteremia: case report. *Tex.Med.* 1986;82(10):35-6.