

Successful Treatment of a Patient with Ventriculoperitoneal Shunt-Associated Meningitis Caused by Extended-Spectrum β -Lactamase-Producing *Klebsiella pneumoniae*

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Bacterial meningitis is responsible for significant morbidity and mortality worldwide, despite that modern antibiotics effectively penetrate cerebrospinal fluid to eradicate bacteria. A clinical suspicion of bacterial meningitis should be recognized early for the rapid diagnostic workup. Bacterial meningitis associated with ventriculoperitoneal shunt (VPS) is not uncommon and infrequently presents as abdominal symptoms and signs. Infections of the central nervous system caused by extended-spectrum β -lactamase-producing *Klebsiella pneumoniae* (ESBL-KP) are extremely rare, and such multiple drug-resistant pathogens frequently cause inappropriate treatments and mortality. β -Lactamases are bacterial enzymes that inactivate β -lactam antimicrobial agents. The increased prevalence of ESBL-producing organism infections has become a worldwide problem. Timely and appropriate treatment is important to reduce mortality and morbidity of infections caused by ESBL-producing organisms. Here, we report a 61-year-old male patient who underwent VPS implantation for consequent hydrocephalus following spontaneous intracranial hemorrhage six months before this presentation. He was admitted for intermittent fever and right lower quadrant abdominal pain, and he was initially managed as acute appendicitis with its typical presentation. Finally, he was diagnosed VPS-associated meningitis caused by ESBL-KP. This patient was successfully treated with the combination of meropenem, a carbapenem antibiotic that is the drug of choice for treating ESBL-producing organisms, and high-dose fosfomycin, a phosphonic acid derivative antibiotic that is effective in treating some drug-resistant pathogens. In the present report, we emphasize the clinical presentations of catheter-related meningitis and risk factors for infections caused by ESBL-producing pathogens. Antibiotic combination therapy can provide synergistic effect and maximize anti-bacterial activity in ESBL-KP meningitis.

Keywords: extended-spectrum β -lactamase; intra-abdominal infection; *Klebsiella pneumoniae*; meningitis; ventriculoperitoneal shunt

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Introduction

β -Lactamases are bacterial enzymes that inactivate β -lactam antimicrobial agents by hydrolysis. Extended-spectrum β -lactamase (ESBL)-producing bacteria are resistant to a broad range of β -lactams, and frequently cause

inappropriate treatments with increased mortality. Infections caused by these organisms are also associated with prolonged hospital stays and increased medical costs (Pitout 2010). The Study for Monitoring Antimicrobial Resistance Trends (SMART) reported that the majority (88.1%) of isolates collected from intra-abdominal infections (IAIs) in the

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Asia-Pacific region were *Enterobacteriaceae* species (Hsueh et al. 2010). ESBL-producing organisms comprised about 13.6% (758 of 5,582 isolates) of *Enterobacteriaceae* isolates. Among the ESBL-producing *Enterobacteriaceae* isolates, *E. coli* was the most common pathogen (63.4%), followed by *Klebsiella pneumoniae* (26.8%) (Sheng et al. 2013).

Bacterial meningitis is responsible for significant morbidity and mortality worldwide, although modern antibiotics effectively penetrate cerebrospinal fluid (CSF) to eradicate bacteria. Nosocomial bacterial meningitis may result from head trauma, post-neurosurgery (e.g., craniotomy, or placement of internal or external ventricular catheters), lumbar puncture, spinal anesthesia, intrathecal drug infusion, or metastatic infection from healthcare-associated bacteremia (van de Beek et al. 2010; Yaita et al. 2012). The incidence of nosocomial bacterial meningitis associated with extra-ventricular drainage (EVD) or ventriculoperitoneal shunt (VPS) is approximately 8% (4-17%) (van de Beek et al. 2010). The most common pathogens causing VPS infection are *Staphylococcus aureus*, Coagulase-negative staphylococci, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* (Wang et al. 2004; Sacar et al. 2006). Meningitis caused by extended-spectrum β -lactamase-producing *Klebsiella pneumoniae* (ESBL-KP) is extremely rare.

Herein, we report a case of VPS-associated meningitis caused by ESBL-KP. The patient was successfully cured with a combination of meropenem and high-dose fosfomycin after surgical removal of the VPS.

Case Report

A 61-year-old male, 164 cm tall and weighing 56 kg, underwent VPS implantation for consequent hydrocephalus following a spontaneous intracranial hemorrhage over the left thalamus about six months before admission. After that, he could maintain general daily activities with only minimal limitations while walking. He was initially admitted for elective surgery of benign prostatic hyperplasia. On the second day of admission, he began to suffer from fever and pain in his right lower abdominal quadrant. Physical examination revealed tenderness and rebounding pain over McBurney's point. Under suspicion of acute appendicitis, a contrast-enhanced computed tomography was performed, which revealed a tubular, blind-end structure about 0.75 cm in diameter arising from the cecal base with mild perifocal fatty stranding, as well as an abscess over the right paracolic region with VPS retention (Fig. 1). He underwent diagnostic laparoscopy, which revealed that the abscess had inflammatory adhesions at the VPS insertion site. The abscess was removed and a concomitant appendectomy performed. Culture of the abscess yielded ESBL-KP. The patient completed a 14-day course of imipenem/cilastatin (500 mg intravenously, every 6 hours) and was then discharged in stable condition.

Three days after discharge, the patient presented to the emergency department with high fever, chills, nausea, vomiting, severe headache, and right lower quadrant abdominal pain. Physical examination revealed a body temperature of 39.8°C, pulse rate of 83 bpm, respiratory rate of 18/min, blood pressure of 147/83 mmHg, drowsy consciousness (Glasgow coma scale: 9), and neck stiffness. He was

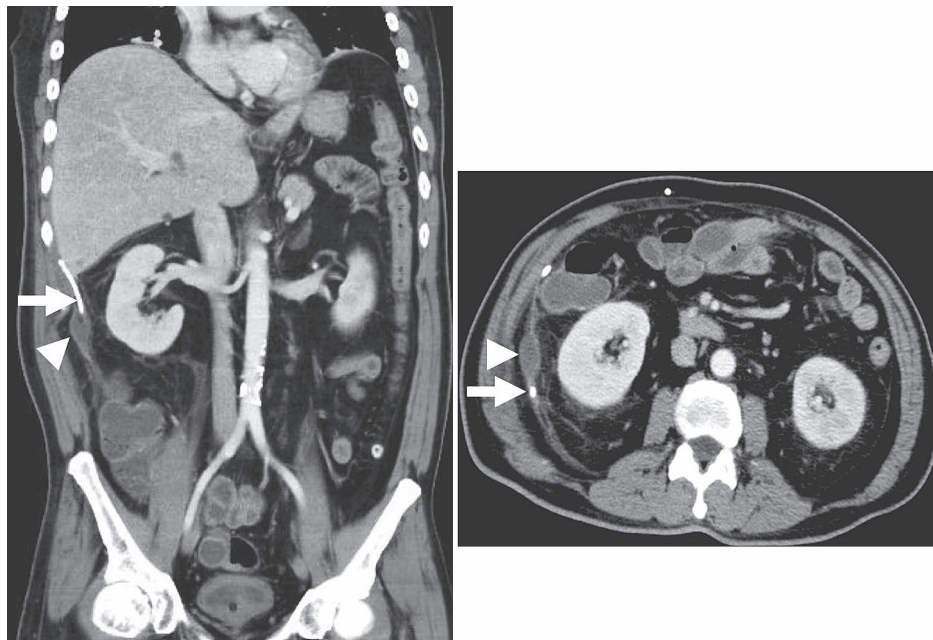


Fig. 1. Contrast enhanced computed tomography of abdomen.

Sagittal view (left panel) and coronal view (right panel) shows a 2.0-cm cystic abscess (arrowhead) over the right paracolic region with ventriculoperitoneal shunt (arrow) retention over the right paracolic gutter.

admitted and a lumbar puncture performed under suspicion of meningitis. The opening pressure was 26 cmH₂O, the CSF was cloudy with polymorphonuclear pleocytosis (white cell count 19,009/ μ L, 90% neutrophils), hypoglycorrhachia (glucose 10 mg/dL), and hyperproteinorachia (total protein 942 mg/dL). The Gram stain of CSF revealed Gram-negative bacilli. Because the recent surgical culture of the intra-abdominal abscess was positive for ESBL-KP, meropenem (1.0 gm intravenously, every 8 hours) was administered for suspected meningitis caused by VPS infection.

The medical history of this patient revealed five episodes of urinary tract infection (UTI) complicated by benign prostatic hyperplasia. He had received several antimicrobial treatment courses in the previous 6 months. Two months before this presentation, he had a UTI episode caused by ESBL-KP.

On the 5th day of admission, CSF culture yielded ESBL-KP. The VPS was removed by a neurosurgeon on the same day; VPS culture also yielded ESBL-KP. The isolates were extremely drug resistant but were still susceptible to carbapenems. Considering the severity of the disease and to better eradicate the ESBL-KP in the CSF, we added fosfomycin (8.0 g intravenously, every 8 hours) in addition to meropenem (1.0 g intravenously, every 8 hours). We also performed an Etest to determine the isolate's susceptibility to fosfomycin and meropenem, which showed mini-

mum inhibitory concentrations (MICs) that were susceptible (Fig. 2A). However, two days after fosfomycin infusion, hypernatremia (154 mmol/L, reference 136-145 mmol/L) developed. Sodium levels returned to normal range (Na 142 mmol/L) after sodium restriction (diet and intravenous fluid). On day 10 of hospitalization, the lumbar puncture was repeated. CSF analysis showed clinical improvement (CSF white cell count 50/ μ L, neutrophils 85%; glucose 39 mg/dL; total protein 500 mg/dL). Gram staining and CSF culture were negative for the pathogen. After 3 weeks of fosfomycin and meropenem combination therapy since last lumbar puncture, the patient was discharged with clear consciousness without significant neurological sequelae. He received weekly outpatient follow-up for the first month and bi-weekly follow-up for the second month. No further signs and symptoms of infection were noted.

Discussion

VPS-associated meningitis may be caused by (a) retrograde infection from the distal end of the shunt, (b) wound or skin breakdown overlying the catheter, (c) colonization of the catheter at the time of surgery, or (d) bacteremia-related metastatic infections. Symptoms and signs include fever, general malaise, or associated with the distal portion of the shunt (i.e., abdominal pain or peritonitis) (van de Beek et al. 2010). A clinical suspicion of bacterial menin-

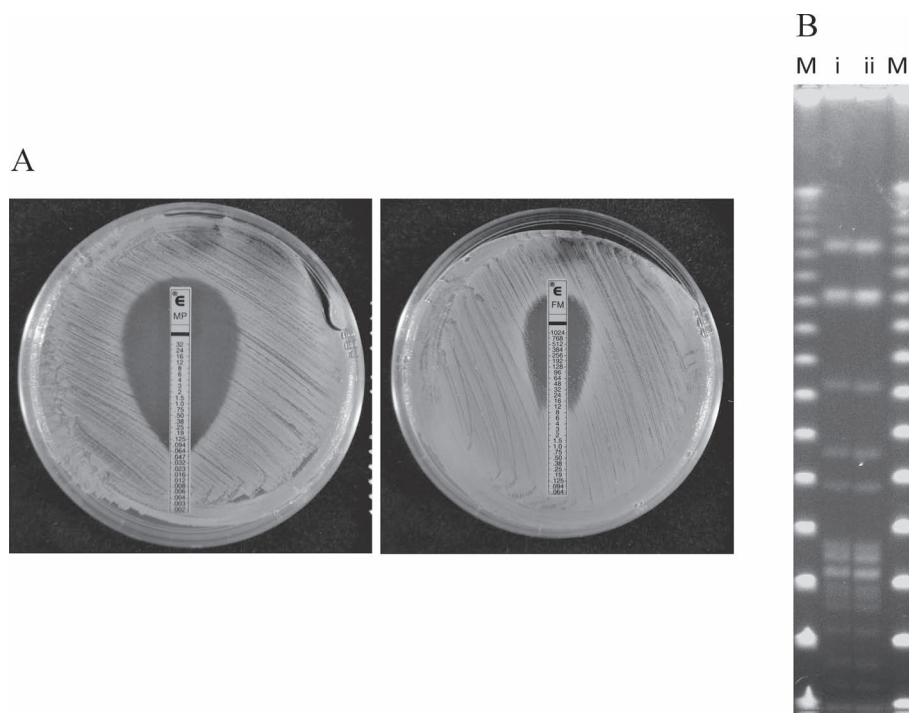


Fig. 2. Etest and Pulsed-field gel electrophoresis.

(A) Etest of the cerebrospinal fluid isolate. The minimum inhibitory concentrations (MICs) of meropenem and fosfomycin are 0.125 mg/L and 64 mg/L, respectively. (Susceptible MIC breakpoints of meropenem and fosfomycin are ≤ 1 and ≤ 64 according to the Clinical and Laboratory Standards Institute, 2013). (B) Pulsed-field gel electrophoresis (PFGE) reveals identical patterns in isolates from cerebrospinal fluid (i) and abscess (ii). M, lambda ladder low-range PFGE molecular mass marker (New England Biolabs, Ipswich, MA, USA).

ginitis should be recognized early for the rapid diagnostic workup and timely antimicrobial therapy (Tunkel et al. 2004). In the present case, the patient had ESBL-KP associated intra-abdominal abscess accompanied by an inflammatory adhesion at the distal end of the VPS. Although the abscess was surgically removed and the patient received a course of effective antimicrobial treatment, the pathogen colonized the VPS, which led to nearly lethal retrograde meningitis. This could be possibly caused by incomplete eradication of the biofilm or organisms. Therefore, VPS should be removed in such condition.

Meningitis infrequently presents as abdominal symptoms and signs (Wang et al. 2004; Conen et al. 2008). The most common clinical presentations of meningitis are fever (78%), neck stiffness (45%), and disturbed consciousness (31%) (Conen et al. 2008). VPS infection-associated IAIs are often diagnosed on image modalities, especially abdominal computed tomography (CT). CT scans often reveal intra-abdominal abscesses, intra-intestinal shunt dislocation, peritoneal cysts, thickened gut walls, and inflammation around the shunt (Conen et al. 2008). In this case, the distal end of VPS had adhesion with the abscess, which mimicked acute appendicitis with its typical presentation as right lower abdominal pain.

The risk factors for infection by ESBL-producing organisms include old age, prolonged hospital stays, previous hospitalizations, previous UTI, malignancies, invasive procedures (such as post-neurosurgery), mechanical ventilation, urinary catheterization, and, most importantly, extended antimicrobial use (Lee et al. 2012; Yaita et al. 2012). The increased prevalence of ESBL-producing organisms in IAI and community-associated infections has become a worldwide problem, particularly in the Asia-Pacific region. ESBL-producers reached 20% prevalence in community acquired-IAI *Enterobacteriaceae* isolates and 80% in healthcare-associated isolates. Among β -lactamase genes contributing to ESBLs, CTX-M is most common, followed by SHV and TEM. We used pulsed-field gel electrophoresis to find that the isolates obtained from the patient's CSF and abscess displayed the same patterns (Fig. 2B). Polymerase chain reaction (PCR) analysis of these isolates revealed CTX-M-14, SHV-1, SHV-11, and TEM-1, compatible with reported epidemic ESBLs distribution in the Asia-Pacific region (Sheng et al. 2013).

Effective antimicrobial agents for infections caused by ESBL-producers are carbapenems (Ramphal and Ambrose 2006). Meropenem is recommended by the Infectious Diseases Society of America (IDSA) treatment guidelines for meningitis, especially when the causative pathogens are ESBL-producing gram-negative bacilli (Tunkel et al. 2004). It is commonly known that meropenem has a broad spectrum of antimicrobial activity, reduced seizure proclivity than imipenem, and penetrates well into many tissues and body fluids including the CSF (Pfausler et al. 2004; Tunkel et al. 2004). The IDSA guideline recommends a 21-day antimicrobial therapy for aerobic gram-negative bacilli

related meningitis (Tunkel et al. 2004). Timely and appropriate treatment is important to reduce mortality and morbidity of infections caused by ESBL-producing organisms (Ramphal and Ambrose 2006).

Fosfomycin, a phosphonic acid derivative (cis-1,2-epoxypropyl phosphonic acid) first described in 1969, was isolated from culture of *Streptomyces* spp (Hendlin et al. 1969). It has a unique mechanism of bactericidal action that inhibits UDP-N-acetylglucosamine enolpyruvyl transferase (MurA), an enzyme that catalyzes the first step in bacterial cell wall synthesis (Eschenburg et al. 2005). Due to its exceptional chemical structure and mechanism of action, fosfomycin seems to be spared from the organisms' various mechanisms for multiple resistances to antibiotics (Arca et al. 1988; Patel et al. 1997; Falagas et al. 2010). In addition, fosfomycin has a low molecular weight and a relatively long half-life (5.7 ± 2.8 hours); as a result, it easily penetrates many tissues, including CSF, and achieves MICs needed to inhibit the growth of most organisms (Falagas et al. 2008). Fosfomycin also has superb activity against ESBL-KP and *E. coli* (de Cueto et al. 2006; Lopez-Cerero et al. 2007; Falagas et al. 2008). A recent review introduced fosfomycin as a reliably active antimicrobial agent against ESBL-producing *Enterobacteriaceae* (Falagas et al. 2010). Pfausler et al. (2004) reported that high-dose fosfomycin (8.0 g, thrice per day) could provide adequate antimicrobial concentrations in the CSF for the entire treatment period and that fosfomycin combined with other classes of antimicrobial agents decreased development of bacterial resistance. Furthermore, fosfomycin combination with carbapenems provided synergistic effect against the ESBL-producing *Enterobacteriaceae* that maximize anti-bacterial activity and also minimize drug resistance (Samonis et al. 2012). In our patient, a prolonged carriage of ESBL-KP was suspected based on previous cultures and a clinical history of prolonged antimicrobial treatments. Furthermore, meningitis occurred after a 2-week course of imipenem to treat an intra-abdominal abscess. For better bacterial eradication, we used a combination of meropenem and high dose fosfomycin for this patient, which achieved good clinical response. However, further randomized controlled studies are required to confirm the efficacy of this combination. Finally, the formulation of intravenous fosfomycin disodium causes a high sodium intake that should be carefully monitored during clinical use (Falagas et al. 2008).

Conclusions

As antimicrobial agents have been widely and extensively used, more and more multidrug-resistant pathogens have emerged, including ESBL-producing *Enterobacteriaceae*. This report describes ESBL-KP meningitis resulting from retrograde VPS infection by intra-abdominal abscess. A combination of meropenem and high-dose fosfomycin achieved good response in this case. Clinicians should be aware of the clinical presentations of meningitis and the risk factors for ESBL producers. Finally, antibiotic combi-

nation therapy may be considered for treating drug-resistant pathogens for its synergistic effect and maximizing antibacterial activity.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

References

- Arca, P., Rico, M., Brana, A.F., Villar, C.J., Hardisson, C. & Suarez, J.E. (1988) Formation of an adduct between fosfomycin and glutathione: a new mechanism of antibiotic resistance in bacteria. *Antimicrob. Agents Chemother.*, **32**, 1552-1556.
- Clinical and Laboratory Standards Institute (2013) *Performance standards for antimicrobial susceptibility testing; 23th informational supplement*, M100-S23, Clinical and Laboratory Standards Institute, Wayne, PA.
- Conen, A., Walti, L.N., Merlo, A., Fluckiger, U., Battegay, M. & Trampuz, A. (2008) Characteristics and treatment outcome of cerebrospinal fluid shunt-associated infections in adults: a retrospective analysis over an 11-year period. *Clin. Infect. Dis.*, **47**, 73-82.
- de Cueto, M., Lopez, L., Hernandez, J.R., Morillo, C. & Pascual, A. (2006) In vitro activity of fosfomycin against extended-spectrum-beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*: comparison of susceptibility testing procedures. *Antimicrob. Agents Chemother.*, **50**, 368-370.
- Eschenburg, S., Priestman, M. & Schonbrunn, E. (2005) Evidence that the fosfomycin target Cys115 in UDP-N-acetylglucosamine enolpyruvyl transferase (MurA) is essential for product release. *J. Biol. Chem.*, **280**, 3757-3763.
- Falagas, M.E., Giannopoulou, K.P., Kokolakis, G.N. & Rafailidis, P.I. (2008) Fosfomycin: use beyond urinary tract and gastrointestinal infections. *Clin. Infect. Dis.*, **46**, 1069-1077.
- Falagas, M.E., Kastoris, A.C., Kapaskelis, A.M. & Karageorgopoulos, D.E. (2010) Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum beta-lactamase producing, Enterobacteriaceae infections: a systematic review. *Lancet Infect. Dis.*, **10**, 43-50.
- Hendlin, D., Stapley, E.O., Jackson, M., Wallick, H., Miller, A.K., Wolf, F.J., Miller, T.W., Chaiet, L., Kahan, F.M., Foltz, E.L., Woodruff, H.B., Mata, J.M., Hernandez, S. & Mochales, S. (1969) Phosphonomycin, a new antibiotic produced by strains of streptomycetes. *Science*, **166**, 122-123.
- Hsueh, P.R., Badal, R.E., Hawser, S.P., Hoban, D.J., Bouchillon, S.K., Ni, Y. & Paterson, D.L.; Asia-Pacific SMART Group (2010) Epidemiology and antimicrobial susceptibility profiles of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in the Asia-Pacific region: 2008 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). *Int. J. Antimicrob. Agents*, **36**, 408-414.
- Lee, Y.L., Chen, Y.S., Toh, H.S., Huang, C.C., Liu, Y.M., Ho, C.M., Lu, P.L., Ko, W.C., Chen, Y.H., Wang, J.H., Tang, H.J., Yu, K.W., Liu, Y.C., Chuang, Y.C., & Liu, C.E. (2012) Antimicrobial susceptibility of pathogens isolated from patients with complicated intra-abdominal infections at five medical centers in Taiwan that continuously participated in the Study for Monitoring Antimicrobial Resistance Trends (SMART) from 2006 to 2010. *Int. J. Antimicrob. Agents*, **40** Suppl, S29-36.
- Lopez-Cerero, L., de Cueto, M., Diaz-Guerrero, M.A., Morillo, C. & Pascual, A. (2007) Evaluation of the Etest method for fosfomycin susceptibility of ESBL-producing *Klebsiella pneumoniae*. *J. Antimicrob. Chemother.*, **59**, 810-812.
- Patel, S.S., Balfour, J.A. & Bryson, H.M. (1997) Fosfomycin tromethamine. A review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy as a single-dose oral treatment for acute uncomplicated lower urinary tract infections. *Drugs*, **53**, 637-656.
- Pfäusler, B., Spiss, H., Dittrich, P., Zeitlinger, M., Schmutzhard, E. & Joukhadar, C. (2004) Concentrations of fosfomycin in the cerebrospinal fluid of neurointensive care patients with ventriculostomy-associated ventriculitis. *J. Antimicrob. Chemother.*, **53**, 848-852.
- Pitout, J.D. (2010) Infections with extended-spectrum beta-lactamase-producing nterobacteriaceae: changing epidemiology and drug treatment choices. *Drugs*, **70**, 313-333.
- Ramphal, R. & Ambrose, P.G. (2006) Extended-spectrum beta-lactamases and clinical outcomes: current data. *Clin. Infect. Dis.*, **42** Suppl 4, S164-172.
- Sacar, S., Turgut, H., Toprak, S., Cirak, B., Coskun, E., Yilmaz, O. & Tekin, K. (2006) A retrospective study of central nervous system shunt infections diagnosed in a university hospital during a 4-year period. *BMC Infect. Dis.*, **6**, 43.
- Samonis, G., Maraki, S., Karageorgopoulos, D.E., Vouloumanou, E.K. & Falagas, M.E. (2012) Synergy of fosfomycin with carbapenems, colistin, netilmicin, and tigecycline against multidrug-resistant *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa* clinical isolates. *Eur. J. Clin. Microbiol. Infect. Dis.*, **31**, 695-701.
- Sheng, W.H., Badal, R.E. & Hsueh, P.R.; SMART Program (2013) Distribution of extended-spectrum β -lactamases, AmpC β -lactamases, and carbapenemases among Enterobacteriaceae isolates causing intra-abdominal infections in the Asia-Pacific region: results of the study for Monitoring Antimicrobial Resistance Trends (SMART). *Antimicrob. Agents Chemother.*, **57**, 2981-2988.
- Tunkel, A.R., Hartman, B.J., Kaplan, S.L., Kaufman, B.A., Roos, K.L., Scheld, W.M. & Whitley, R.J. (2004) Practice guidelines for the management of bacterial meningitis. *Clin. Infect. Dis.*, **39**, 1267-1284.
- van de Beek, D., Drake, J.M. & Tunkel, A.R. (2010) Nosocomial bacterial meningitis. *N. Engl. J. Med.*, **362**, 146-154.
- Wang, K.W., Chang, W.N., Shih, T.Y., Huang, C.R., Tsai, N.W., Chang, C.S., Chuang, Y.C., Liliang, P.C., Su, T.M., Rau, C.S., Tsai, Y.D., Cheng, B.C., Hung, P.L., Chang, C.J. & Lu, C.H. (2004) Infection of cerebrospinal fluid shunts: causative pathogens, clinical features, and outcomes. *Jpn. J. Infect. Dis.*, **57**, 44-48.
- Yaita, K., Komatsu, M., Oshiro, Y. & Yamaguchi, Y. (2012) Post-operative meningitis and epidural abscess due to extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*: a case report and a review of the literature. *Intern. Med.*, **51**, 2645-2648.