Evaluation Criteria and Rationality Analysis of Drug Utilization of Meropenem in a Tertiary Medical Institution in Beijing

Zhang Qiming, Huang Zhe*

(School of Business Administration, Shenyang Pharmaceutical University, Shenyang 110016, China)

Abstract

Objective To establish a drug use evaluation (DUE) standard for meropenem in a tertiary medical institution in Beijing, and to analyze the use of meropenem for promoting the rational use of antibiotics. **Methods** A criteria of DUE of meropenem was established based on drug instructions, related guidelines and experts' opinions. Then, 120 cases of meropenem use from January to December 2021 were selected to carry out a retrospective study. **Results and Conclusion** 120 cases of meropenem use involved 8 clinical departments, including 38 cases in the Department of Respiratory Medicine, 25 cases in the Department of Tuberculosis, and 20 cases in the Department of Gastroenterology. The detection rate of pathogenic microorganisms before first use was 79.17%, and the clinical treatment effectiveness rate was 81.67%. The irrational use of meropenem included poor grasp of usage indications, excessively high starting points, inappropriate usage and dosage, non-standard treatment courses, and excessive combination medication. Pharmacists should strengthen the monitoring and evaluation of carbapenem drugs such as meropenem, provide timely feedback on relevant situations, and promote rational clinical medication.

Keywords: meropenem; antibiotics; rational use; drug use evaluation

Meropenem is an artificially synthesized β-Lactam antibiotics, belonging to the second-generation broad-spectrum carbapenem antibiotics, having characteristics of wide antibacterial spectrum, strong antibacterial activity, good clinical efficacy, and few adverse reactions. Since it can produce ultra-broad spectrum β-Lactamase stability, it is widely used in clinical practice [1, 2]. Its antibacterial mechanism is through covalent bonding with penicillin binding proteins involved in cell wall synthesis, thereby inhibiting the synthesis of bacterial cell walls, causing cell expansion and rupture, playing an antibacterial and bactericidal role. It is sensitive to both Gram-positive and Gram-negative bacteria, especially with strong antibacterial effects on Gram-negative bacteria. Therefore, it is commonly used to treat diseases such as severe infections and multiple infections. Due to its high price and susceptibility to abuse, carbapenems, as a special grade antibacterial drug, have always been a key monitoring drug in this medical institution due to their potential to induce bacterial resistance. Therefore, it is necessary to conduct a reasonable investigation into its current use status. Drug use evaluation (DUE) is a concept proposed by the American Society of Hospital Pharmacists (ASHP) in 1987. It refers to the rational evaluation of drug selection, dosage, and other aspects in the clinical medication process, based on predetermined relevant standards [3, 4], to ensure the rationality, safety,

* Corresponding author: Huang Zhe, professor. Major research area: Drug regulatory science and pharmaceutical management, etc. Tel: 024-23986543, E-mail: huangzhe2000@sina.com.

and effectiveness of drug use, and thereby improve the level of medical service for patients [5]. A DUE standard was established in this medical institution for meropenem and an investigation and analysis of its use was conducted to evaluate whether clinical medication use is reasonable, which can also provide reference for the standardized use of meropenem.

1 Materials and methods

1.1 Sources of data

120 medical records of discharged patients who used meropenem in 2021 from the medical institution's information management system (HIS) were randomly selected, and the case information was recorded item by item according to the requirements of the questionnaire. The content included the patient's medical record number, gender, age, clinical diagnosis, hospitalization time, medication time, usage and dosage, solvent, course of treatment, combination medication, incompatibility, and pathogen culture adverse reactions. Finally, clinical efficacy evaluations were summarized and analyzed in an Excel spreadsheet.

1.2 Research method

A retrospective analysis was conducted on the relevant information of 120 medical records of the medical institution according to the drug instructions of meropenem, the "Notice on Further Strengthening the Management of Clinical Application of Antibiotic" (National Health Commission [2015] No. 42) [6], and the "Notice on Issuing the Expert Consensus on Clinical Application of Carbapenems Antibiotics" (National Health Commission [2018] No. 822) [7], the "Guiding Principles for the Clinical Application of Antibiotics" (2015 Edition) [8], the "National Guidelines for Antibiotic Therapy" (Third Edition), and the "New Pharmacology" (18th Edition). An expert consultation method was used to establish a DUE standard suitable for the clinical use of meropenem in this medical institution through multiple discussions with the hospital antibacterial drug management expert group composed of clinical, infection, pharmacy, microbiology, and other disciplines. Then, the survey results were put into an Excel spreadsheet for analysis.

1.3 Evaluation criteria for DUE of meropenem

With China's relevant policies and regulations, guideline consensus and drug instructions, the data of this thesis are judged by standardized criteria. Establishment of medication evaluation criteria for DUE of meropenem, as shown in Table 1 for specific distribution.

Table 1 Evaluation criteria for drug utilization of meropenem

Evaluation index	Evaluation item	Index content
Management index	Consultation system	(1) Timely request the hospital or outside the hospital special use of antibiotics consultation experts for consultation and have consultation records;
		(2) In accordance with the provisions of the National Health Office [2017] No. 10 document for special file registration management;
		(3) Regular training, assessment and records shall be kept for doctors who are granted the right to prescribe antibiotics for special use
	Physician's authority	(1) Medical orders shall be issued by doctors with the right to prescribe antibiotics for special use, and must be supported by information technology;
		(2) It can be used in special circumstances;
		(3) Use of leapfrog is limited to 24 hours, and the corresponding course of disease is recorded

(to be continued)

Continued Table 1

<table>
<tr><th>Evaluation index</th><th>Evaluation item</th><th>Index content</th></tr>
<tr><td></td><td>Course record</td><td>(1) If the patient needs to use antibiotics, the relevant use records should be kept;
(2) Doctors must have relevant records of the course of illness when giving medical orders, adjusting doses, or stopping the drug</td></tr>
<tr><td>Drug using index</td><td>Indication</td><td>(1) It is suitable for adults and children who are infected by a single or multiple meropenem sensitive bacteria; Pneumonia (including nosocomial pneumonia), urinary tract infections, intra-abdominal infections, gynecological infections (such as endometritis, pelvic inflammatory disease), skin and soft tissue infections, meningitis, and septicemia;
(2) For the empirical treatment of adult granulocytopenia with fever, it can be used alone or in combination with antiviral drugs or antifungal drugs;
(3) For the treatment of multiple infections, it can be used alone or in combination with other antimicrobials</td></tr>
<tr><td></td><td>Route of administration and infusion time</td><td>(1) Intravenous injection: The time should be greater than 5 minutes;
(2) Intravenous infusion: the time is greater than 15−30 minutes</td></tr>
<tr><td></td><td>Solvent selection</td><td>(1) Intravenous injection: The powder injection is prepared with sterile water for injection as a solution with a concentration of about 50 mg/mL;
(2) Intravenous infusion: The powder injection is prepared with 0.9% sodium chloride injection as a solution with a concentration of 1−20 mg/mL, and the solution should be used within 6 hours at room temperature (the drug solution cannot be frozen); With 5% glucose injection, glucose sodium chloride injection, prepared as a concentration of 1−20 mg/mL solution, need to use immediately</td></tr>
<tr><td></td><td>Usage and dosage</td><td>(1) Pneumonia, urinary tract infection, gynecological infection (such as endometritis), skin and soft tissue infection every 8 hours, 500 mg each time, intravenous drip;
(2) In the treatment of nosocomial pneumonia, peritonitis, neutropenia patients with infection and sepsis, the drug should be given once every 8 hours, 1 g each time, intravenous drip;
(3) For patients with meningitis, it is recommended to give the drug once every 8 hours, 2 g each time, intravenous drip or push;
(4) In adult patients with renal insufficiency, the dose should be adjusted according to creatinine clearance (Ccr)
<table>
<tr><th>Creatinine clearance (mL/min)</th><th>Dose (Depending on the type of infection)</th><th>Time interval</th></tr>
<tr><td>26−50</td><td>1 recommended dose</td><td>every 12 hours</td></tr>
<tr><td>10−25</td><td>1/2 recommended dose</td><td>every 12 hours</td></tr>
<tr><td>< 10</td><td>1/2 recommended dose</td><td>every 24 hours</td></tr>
</table></td></tr>
<tr><td></td><td>Special population</td><td>(1) It should be used with caution in pregnant patients, and breastfeeding should be avoided during administration; For children 3 months to 12 years of age, the recommended dose should be 10-20mg/kg/q8h per dose, depending on the type and severity of infection, susceptibility to pathogenic bacteria, and the patient’s condition;
(2) The recommended dose for treating meningitis in children is 40 kg/q8h each time; For children weighing > 50 kg, it can be administered as an adult dose;
(3) For adult patients with renal dysfunction, the frequency of administration should be adjusted according to creatinine clearance</td></tr>
</table>

(to be continued)

Continued Table 1

Evaluation index	Evaluation item	Index content
	Drug combination	Use it in combination with other antimicrobials, and the indications should conform to the expert consensus on the clinical application of carbapenems and the Guidelines for Clinical Application of Antimicrobials
	Incompatibility	(1) Meropenem and other carbapenems should not be used in allergic patients; (2) Contraindicated in patients using sodium valproate
	Adverse reaction	(1) Observe and record the adverse reactions of patients in the process of using the antimicrobial drug meropenem and do timely treatment; (2) The main adverse reactions were allergy, diarrhea, abnormal liver function, increased serum creatinine, abnormal platelet change, double infection, etc.
Laboratory indicators and prognosis	Etiological examination	(1) Before the use of antibiotics, the corresponding etiology should be sent for examination, and the laboratory test rate should be > 80%; (2) Meropenem should be evaluated by dynamic laboratory tests during treatment, such as blood routine, procalcitonin and bacterial culture; Patients with continuous use for more than 1 week should be examined for liver function
	Course of treatment	(1) The general course of treatment is 3−14 days, which can be extended according to the severity of infection; (2) The efficacy was evaluated after 3−5 days of empirical use
	Treatment outcome	(1) Recovery: Clinical symptoms disappear, no abnormal signs, no abnormal examination results; (2) Improvement: the clinical symptoms basically disappeared, and some examination indicators were abnormal but approaching normal; (3) Ineffective: Clinical symptoms did not significantly improve or worsen

2 Results

2.1 Basic information of patients

Among the 120 cases in this review, 74 were males (61.7%) and 46 were females (38.3%), aged from 28 to 97 years old, with an average age of 76.8. Most of them were elderly patients, and 101 were over 65 years old, accounting for 84.2%. The duration of hospitalization was 4−232 days.

2.2 Distribution of departments

This review mainly involves 22 departments in the medical institution, among which the top three are ICU, Department of Hematology and Department of Respiratory Medicine, as shown in Table 2 for specific distribution.

2.3 Distribution of infection sites

In this review, meropenem was mainly used in the treatment of lung infection, 84 cases (70.0%), 15 cases (12.5%) of bloodstream infection, 8 cases (6.7%) of urinary system infection, 3 cases (2.5%) of abdominal cavity infection, 3 cases (2.5%) of intracranial infection, and 3 cases (2.5%) of skin and soft tissue infection, with a rational rate of 96.7%. It is in line with the indications of meropenem, indicating that the doctors of the medical institution have a good grasp of the overall indications of meropenem. However, there are also some cases with unreasonable indications or high starting point of use, indicating that the medical institution still has lax control of the indications of meropenem. There is the possibility of abuse, and doctors should pay more attention to this problem.

Table 2 Distribution of meropenem use in different departments

Clinical department	*n*	Constituent ratio (%)	Clinical department	*n*	Constituent ratio (%)	Clinical department	*n*	Constituent ratio (%)
ICU	24	20	Neurosurgery	4	3.3	Chest Pain Center	2	1.7
Department of Hematology	16	13.3	Emergency Department	3	2.5	EICU	1	0.8
Respiratory Medicine	15	12.5	Vascular Surgery	3	2.5	Palliative Care	1	0.8
Comprehensive Geriatrics	9	7.5	CCU	2	1.7	Department of Infectious Diseases	1	0.8
Department of Neurology	8	6.7	Rehabilitation Department	2	1.7	Hyperbaric Oxygen Department	1	0.8
Medical Oncology	8	6.7	General Surgery Department	2	1.7	Urology	1	0.8
General Practice	7	5.8	Nephrology Department	2	1.7			
Department of Cardiology	6	5	Gastroenterology Department	2	1.7			

2.4 Management indicators

A retrospective analysis of 120 cases was conducted, all of which were prescribed by doctors in antibiotics authority. 94 of them recorded the reasons for starting the use of the drug, adjusting the dose after use, and stopping the drug in detail during the course of the disease (rational rate 78.3%). They were in line with the national guidelines for the clinical use of antimicrobials, indicating that the medical institution attached importance to the management of antimicrobials.

2.5 Laboratory test indicators

Out of 120 cases, a total of 184 were sent for pathogen examination, and 122 cases were detected as pathogens. Among them, 108 were sent for examination before administration (with a reasonable rate of 90.0%), and 12 were sent for pathogen examination after administration (with an unreasonable rate of 10.0%). Doctors had a strong awareness of pre-medication testing and complied with the medical institution's regulations on the pre-medication testing rate for special grade antibacterial drugs. However, 46 positive pathogens were cultured in the samples submitted for examination, with a positive rate of 40.4%, which was not high. The main reason might be that medical staff had insufficient knowledge of the timing, location, and transportation ability of sample collection during the examination process. The hospitalized patients were mostly elderly people, who had been hospitalized for a long time and used antibiotics for a long time, resulting in the inhibition of sensitive bacteria. In this review, the number of positive strains in descending order was Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter baumannii, Enterobacter cloacae, Escherichia coli, Stenotrophomonas maltophilia, etc. Only 6 out of 120 cases had detailed reasons for choosing meropenem based on drug sensitivity results and patient condition analysis, as well as the basis for discontinuation, in the course records. Physician cases were not described in detail, and regular training and supervision of physicians should be strengthened. The specific content is shown in Table 3 and Table 4.

Table 3 Distribution of specimens submitted for examination

Specimen sent for testing	*n*	Ratio of composition (%)	Specimen sent for testing	*n*	Ratio of composition (%)	Specimen sent for testing	*n*	Ratio of composition (%)
Phlegm	80	43.5	Whole blood	38	20.7	Urine	29	15.8
Bronchoalveolar lavage fluid	22	11.9	Catheter	9	4.8	NGS	2	1.1
Cerebrospinal fluid	2	1.1	Hydrothorax and ascites	2	1.1			

Table 4 Distribution of pathogens

Pathogen	*n*	Ratio of composition (%)	Pathogen	*n*	Ratio of composition (%)	Pathogen	*n*	Ratio of composition (%)
Pseudomonas aeruginosa	29	23.8	Klebsiella pneumoniae	20	16.4	Acinetobacter baumannii	16	13.2
Staphylococcus aureus	12	9.8	Enterobacter cloacae	7	5.7	Escherichia coli	6	4.9
Candida albicans	5	4.1	Burkholderia cepacia	5	4.1	Proteus mirabilis	4	3.3
Stenotrophomonas maltophilia	4	3.3	Enterococcus faecium	3	2.5	Serratia marcescens	3	2.5
Enterococcus faecalis	2	1.6	Listeria monocytogenes	2	1.6	Morganella morganii	2	1.6
Staphylococcus haemolyticus	2	1.6						

2.6 Medication process

In the review of 120 cases, 10 cases were found to be unsuitable for the use of meropenem, with a reasonable rate of 91.7%. A total of 21 cases were found to be unsuitable for combination therapy, with a reasonable rate of 82.5%. The coincidence rate of liver and kidney function tests before and after medication was 70.83%, and 29.17%, respectively. Other cases did not undergo relevant liver and kidney function tests after one week of medication. The coincidence rate of treatment course was 79.16%. In this survey, the vast majority of doctors were able to timely grasp and accurately use the dosage of meropenem, but there were also a few cases of unreasonable use. The specific manifestations are as follows: (1) The frequency of administration is not standardized. Meropenem requires a long period of time to maintain an appropriate blood concentration to kill sensitive bacteria. It is a time-dependent antibacterial drug with a half-life of about 1 hour. Some doctors prescribed the frequency of administration as TID, and even in the absence of liver and kidney function abnormalities. Some medical staff set the frequency of administration as QD or BID, resulting in insufficient maintenance time of effective treatment blood concentration and weakened treatment effectiveness. (2) The single dose is relatively low. For patients with severe sepsis, septic shock, and other severe infections, a single dose should not be less than 1.0 g. (3) When patients experience liver and kidney dysfunction, doctors do not adjust the dosage based on the patient's creatinine clearance rate, which leads to drug accumulation in the body and increases the incidence of adverse reactions. If a male patient is 90 years old and has a relatively light weight, their creatinine clearance rate is calculated to be 12.78 mL/min, and the doctor should give a dosage of 1.0 g of meropenem, q12 h, and intravenous infusion. According to the DUE guidelines of the medical institution, elderly patients with renal insufficiency undergo blood routine tests for creatinine 287 after admission μmol/L, the recommended dose of meropenem is 0.5 g, q12 h, and intravenous drip. The dosage for this patient is much higher and should be reduced. (4) 20.83% of unreasonable drug use is due to the use of treatment courses and prolonged medication duration. According to the survey, some patients at this medical institution had been using meropenem for a long time, up to 45 days. The main symptoms were that the patient's condition had improved significantly and they had not stopped using meropenem in a timely manner, or that the patient's body temperature, white blood cell count, neutrophil count, C-reactive protein, and procalcitonin had returned to normal for more than 3 days. However, some doctors did not stop the medication or lower the treatment ladder in a timely manner until discharge. As is well known, long-term use of powerful broad-spectrum antibacterial drugs can easily lead to bacterial resistance and dysbiosis, and in severe cases, it can lead to secondary infections, increase the probability of adverse reactions, and seriously increase the economic burden on patients. Therefore, the treatment course of special use of grade antibiotics such as meropenem is a key point that the medical institution should focus on in the next step. (5) Repeated drug use accounted for 8.33% of unreasonable drug use. The main manifestation was that there was overlap in the antibacterial spectrum of antibiotics used by individual patients. It should be noted that piperacillin sodium/tazobactam sodium, ceftriaxone, and cefoxitin sodium all belong to *β*-Lactam antibiotics that have the same mechanism of action as meropenem, and their antibacterial spectrum overlaps. Combination therapy can increase the incidence of adverse reactions and easily increase the economic burden on patients.

2.7 Treatment effect and adverse reactions

The results of this survey show that 69 patients in this medical institution improved their treatment efficacy after using meropenem, with an effectiveness rate of 57.5%. The patients who did not receive effective and expected treatment were mostly elderly patients, with many underlying diseases, low immunity, renal dysfunction, mixed blood diseases or tumors, or may be related to the lack of targeted clinical use of the drug. In terms of adverse reactions, a total of 6 adverse reactions occurred in 120 patients, mainly including 2 cases of rash, 2 cases of liver function damage, and 2 cases of renal function damage. Most cases improved after receiving targeted treatment after discontinuation of medication. It should be noted that if the patient needs to receive meropenem for a long time, close attention should be paid to whether there are any abnormalities in the patient's abdomen and bowel movements, and efforts should be made to detect them as soon as possible to avoid bacterial imbalance caused by diarrhea.

3 Discussion

The ASHP developed the concept of DUE in 1987 [9]. Based on the drug utilization review (DUR), it has been gradually refined in practice. The establishment of DUE criteria combined with the authority of clinical basis and the actual situation of the unit, it can not only provide theoretical and technical support for medical staff, but also well combine academic behavior and administrative means. Compared with the simple administrative intervention, it is more acceptable to medical staff and conducive to clinical rational drug use. The medical institution has established a set of systematic and comprehensive evaluation criteria for meropenem from 14 dimensions of management indicators, drug use indicators, laboratory indicators and prognosis. However, the survey results show that there is still a gap between some target values and expected target values. In the next stage, the microbiology department of the medical institution needs to strengthen the knowledge training of microorganisms, improve the laboratory hardware facilities, the inspection rate and qualified specimens, so as to improve the positive culture rate of bacteria, which can make the clinical rational application of antibiotics more effectively. Besides, we should strengthen the training of clinicians and drug management to ensure that the selection of drugs is in accordance with the special grade antibacterial drug application guidelines. For the target pathogens, symptomatic drugs should be prescribed to reduce the common drug model. In addition, we should strengthen the drug control of meropenem to reduce the abuse of antibacterial drugs to a certain extent.

Meropenem should not be used at the same time with other drugs because they have safety risks. Meanwhile, prescription intervention should be strengthened to avoid adverse drug reactions. It is reported that the adverse reactions of this kind of drugs are related to the concentration. If the drop speed is too fast, the patient may have dizziness, fatigue, nausea, vomiting and other adverse reactions. Therefore, it is suggested that appropriate infusion time should be set for same dose of clinical drip, such as slow infusion or pump, which will improve the therapeutic effect [10]. In addition to the related adverse reactions recorded in the instructions, meropenem has been reported to cause platelet elevation, neutropenia, heart failure and cholestatic liver injury [11-14], which should be paid attention. Therefore, it is suggested that in addition to improving the hardware facilities such as microbial culture room, hospitals should also strengthen the training of the majority of medical staff on the rational use of antibiotics to avoid the generation of drug-resistant bacteria.

To sum up, meropenem is a kind of antibiotics that is expensive and may induce drug resistance. Therefore, in clinical use, it is necessary to strictly control the drug use [15-17], improve the detection rate of pathogenic microorganisms, increase the target treatment, and avoid the generation of drug-resistant bacteria. In addition, special file management can be included in the future DUE evaluation of meropenem, and then practical operation and clinical practicability should be strengthened, which can promote the clinical rational use of meropenem.

References

[1] Xie Benshu. Research progress on the clinical application of meropenem, a novel carbapenem antibiotic [J]. Chinese Pharmacy, 2011, 22 (5): 78-81.
[2] Liu Shurong. Clinical application and adverse reactions of meropenem [J]. Chinese Community Physician (Bimonthly Medical Specialty), 2009, 11 (3): 6-7.
[3] Shi Qingping, Xu Shanchu, Liu Yan, et al. Establishment and application of working model of DUE clinical pharmacy [J]. Chinese Pharmacy, 2010, 21 (22): 2104-2106.
[4] Wang Wenwen, Lou Haikui, Wang Jun, et al. Application and empirical study of DUE model in clinical pharmacy [J]. Chinese Journal of Modern Pharmaceutical Application, 2016, 10 (4): 276-277.
[5] Su Qiang, Long Enwu, Tang Zhili, et al. Application and empirical study of DUE model in the special remediation of antibiotics [J]. Chinese Pharmacists, 2014, 17 (4): 630-632.
[6] National Health and Family Planning Commission, Medical Administration Bureau. Notice on issuing 3 technical documents including "Expert Consensus on Clinical Application of Carbapenem Antibiotics" [J]. China Emergency Management, 2017, 3 (2): 38-39.
[7] Zhang Wenshan. Effect of intravenous injection of meropenem combined with inhalation in the treatment of ventilators associated pneumonia [J]. Heilongjiang Medicine, 2017, 30 (2): 335-337.
[8] Li Qiushi. Clinical study of meropenem in the treatment of neonatal severe multi-drug resistant bacteria infection [J]. China Pharmaceutical, 2017, 26 (2): 60-64.
[9] Li Xiaomin, Sun Yu, Liang Yongli, et al. Comparative analysis of imipenem cilastatin sodium and meropenem in the treatment of intracranial infections after craniotomy [J]. Chinese Journal of Hospital Pharmacy, 2016, 4 (16): 1396-1400.
[10] Li Zhiqiang, Wang Guanda, Huang Yan, et al. Systematic evaluation of delayed and intermittent infusion of meropenem in the treatment of severe infection patients [J].

Chinese Journal of Hospital Pharmacy, 2017, 37 (2): 155-160.

[11] Huang Baokun, Li Shengpeng, Wang XingYu. Meropenem for injection induced platelet elevation: A case report [J]. Journal of Practical Gynecologic Endocrinology (Electronic edition), 2018, 51 (9): 181-184.

[12] Chen Meng. Meropenem induced severe heart failure adverse reaction: A case report [J]. Chinese Modern Applied Pharmacy, 2018, 35 (9): 1419.

[13] Ma Jie, Wang Nan, Zhang Sixi, et al. Meropenem induced neutrophil deficiency: A case report [J]. Medical Review, 2018, 37 (6): 769-770.

[14] Xing Gang, Liu Xiaoling, Huang Jianhua. Meropenem induced cholestatic liver injury: A case report [J]. Medical Review, 2018, 37 (7): 913-914.

[15] Li Tao, Lu Miao. Cefoperazone and sulbactam combined with meropenem or etamycin in the treatment of pan drug-resistant acinetobacter baumannii pneumonia [J]. Journal of Clinical Rational Drug Use, 2018, 11 (20): 4-6.

[16] Liu Xiaoli, Fang Ling, Zhu Minghua, et al. Meropenem and ceftriaxone in the prevention and treatment of nosocomial infection in patients with cirrhosis complicated with upper gastrointestinal bleeding [J]. Journal of Practical Hepatology, 2018, 21 (4): 593-596.

[17] Xie Yi, Wang Jin, Liu Zhifang, et al. To study the clinical effect of meropenem in the treatment of neonatal bacterial meningitis [J]. Heilongjiang Medicine and Pharmacy, 2018, 31 (4): 797-798.