

Analysis of the Pathogens and the Use of Anti-bacteria's in Patients with Nosocomial Infection at an Oncological Neurosurgery Department

Lianzhen Chen^{1*}, Dongqi Zhang¹, Jianxin Kong², Yanting Wang¹, Yujuan Zhang³, Jincheng Yang¹, Baomin Chen⁴, Wei Cui³, Jinghai Wan^{2*}, Guohui Li^{1*}

¹Department of Pharmacy, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, P.R.China.

²Department of Neurosurgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, P.R.China.

³Department of Clinical Laboratory, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, P.R.China.

⁴Disease and Infection Control Office, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, P.R.China.

Research Article

*Corresponding author

Lianzhen Chen,
Dept. of Pharmacy,
Chinese Academy of Medical
Sciences and Peking Union Medical
College, Beijing 100021, P.R.China.

Jinghai Wan,
Dept. of Neurosurgery, Chinese
Academy of Medical Sciences and
Peking Union Medical College,
Beijing 100021, P.R.China.

Guohui Li,
Dept. of Pharmacy,
Chinese Academy of Medical
Sciences and Peking Union Medical
College, Beijing 100021, P.R.China.

Article Information

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Abstract

Aim: To explore the rationality of antibacterial application and the occurrence of infection in the cancer hospital, especially when it was subdivided incision infection and intracranial infection, both of which were together counted as Surgical Site Infection (SSI) before.

Methods: A retrospective analysis was conducted in 51 brain tumor patients with infection after craniotomy from January 1, 2016 to December 31, 2016. The detailed information was recorded for statistical analysis. We set a database to investigate and evaluate the distribution of pathogens and rationality of prophylactic use of antibacterials.

Results: A total of 44 pathogenic bacteria were isolated. There were 5 gram-positive bacteria (71.4%) and 2 gram-negative bacteria (28.6%) causing incision infection; there were 5 gram-positive bacteria (50.0%) and 5 gram-negative bacteria (50.0%) causing intracranial infection. The most widely-used antibacterial was Piperacillin/Sulbactam.

Conclusion: Prophylactic antibacterial agent selection, administration timing and duration during perioperative period of tumor neurosurgery should be adjusted to reduce nosocomial infection.

Keywords: Neurosurgery; Nosocomial Infection; Pathogen; Antibacterial; Perioperative

Key messages

What is already known on this subject

- The nosocomial infection rate of oncological neurosurgery patients in perioperative period is relatively high.
- It is important to prophylactically use antibacterial agents during the perioperative period.

What the study adds:

The data of the distribution of the pathogens were divided into two subgroups, incision infection and intracranial infection groups, both of which were together counted as surgical site infection (SSI) before. Our statistical strategy will provide more details of the nosocomial infection and be an important reference for clinical application of antibacterial agents.

We separately analysed and discussed Type-I and Type-II incisions to shed light on advanced pharmaceutical care.

We explored the constituent and distribution of the pathogens, the relation between prophylactic use of antibacterial agents and infection rates, and we proposed the timing of prophylaxis and the selection of antibacterial agents, which will contribute to reduction of nosocomial infection.

Introduction

Central nervous system infections in patients undergoing neurosurgical procedures increases morbidity and mortality [1]. Cancer Hospital Chinese Academy of Medical Sciences is a national landmark tumor specialized hospital, which integrates with treatment, education, research, and prevention, and carries out all-around tumor related basic research and clinical diagnosis. The features of the department of neurosurgery are mainly treating intracranial tumors, skull base tumors, intraspinal tumors and cerebral aneurysm. Based on historical data, the proportion of tumors of skull base surgery proportion was as high as 40% and most surgeries belonged to the type-II incision operation with long surgery duration. In addition, the proportion of brain metastatic tumor operation was higher than that in general hospitals. Patients with brain metastatic tumor were often treated with surgery, radiotherapy and chemotherapy. Patients who have brain tumors with neurosurgical operation were subject to be infected easily if antibacterial agents were not appropriately given. This will lead to the deterioration of the patient condition [2]. By analysing pathogenic distribution, antibacterial susceptibility and application state, we explored the rationality of antibacterial application and the occurrence of infection in the cancer hospital, and subdivided infection to incision infection and intracranial infection, both of which were of no distinction before. Based on these, we may propose appropriate measures on reasonably applying antibacterial agents so as to reduce postoperative infection rate.

Materials and Methods**Data Source and Methods**

A retrospective investigation was conducted on nosocomial infection patients, including 26 male and 25 female, who were given craniocerebral operations from January 1, 2016 to December 31, 2016 in the department of neurosurgery of our hospital. The age ranged from 5 to 77 years old, and the average age was 45.12±16.61.

Data Collection

The medical record system was reviewed. Nosocomial infection cases reported to Disease and Infection Control Office of our hospital from January 01, 2016 to December 31 were included. The information of patients' operative incision type, operating duration, infectious sites (including incision, intracranial, lungs, urinary tract, and blood-stream), and perioperative prophylactic use of antimicrobial agents was collected.

Pathogens isolation and antimicrobial susceptibility testing

Clinical specimens were inoculated in blood agar plates, Chinese blue agar plate and Chocolate agar plate, and cultured

at 37°C for 18~24h. All the selected isolates were obtained and stored at -80°C. Then they were recovered and grown overnight on blood agar plates at 37°C. All the bacterial isolates were confirmed by use of VITEK2 Compact (BioMe'rieux) and Phoniex-100 (BD) automated systems. Antimicrobial Susceptibility (AST) profiles were also determined by the two automated systems and also reviewed by the agar dilution method on Mueller-Hinton agar. Clinical and Laboratory Standards Institute (CLSI) breakpoints were used for MIC interpretation. *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality controls in each set of tests.

Clinical specimens were inoculated in Potato Dextrose Agar and cultured at 28°C for 18~24h. The fungus were confirmed by CHROMAgr™ *Candida* and VITEK2 Compact. AST were determined by the agar dilution method (ATB fungus2). CLSI breakpoints were used for MIC interpretation. The morphological identification of filamentous fungi was carried out by transparent adhesive tape. Until now, our hospital has not carried out the AST for filamentous fungi.

Data Analysis

The collected data were compiled, tabulated, and analysed with Microsoft Excel Professional 2013.

Results**Basic Information of Infection**

From January 1, 2016 to December 31, 2016, the Department of Neurosurgery in our hospital received 390 surgical patients, during which there were 51 patients (13.08%) and 56 infections occurred. The average C-reactive protein is 5.8 mg/dl. The distribution of infection sites with different types of incision was shown in Table 1.

Table 1: Infectious site distribution of different types of incision

Infection site	I incision surgery	II incision surgery
Intracranial	8 (42.1%)	22 (59.5%)
Lungs	4 (21.0%)	6 (16.2%)
Incision	3 (15.8%)	3 (8.1%)
Urinary tract	3 (15.8%)	3 (8.1%)
Blood	1 (5.3%)	3 (8.1%)
Total	19 (100%)	37 (100%)

Constituent of Pathogens

Nighty-three specimens had been tested in 51 nosocomial infection patients with neurosurgery. Forty-four pathogenic bacteria were isolated. The detection rate was 47.31%. Specimens

were from cerebrospinal fluid, incision secretion, blood, urine and sputum. The detected pathogens from patients with different types of incision were shown in Table 2.

Table 2: Pathogens Situation with different types of incision operation.

Species	Pathogens	I incision surgery (rate)	II incision surgery (rate)	Sum(rate)	Total
G ⁻	Klebsiella Pnenmoniae	4(57.1%)	3(42.9%)	7(15.91%)	26/44 (59.10%)
	Escherichia co1i	0(0%)	5(100%)	5(11.36%)	
	P.Aeruginosa	0(0%)	3(100%)	3(6.82%)	
	Salmonella	3(100%)	0(0%)	3(6.82%)	
	Stenotrophomonas Maltophilia	0(0%)	3(100%)	3(6.82%)	
	Acinetobacter Baumannii	1(50.0%)	1(50.0%)	2(4.54%)	
	Klebsiella oxytoca	1(50.0%)	1(50.0%)	2(4.54%)	
G ⁺	Bacillus mirabilis	1(100%)	0(0%)	1(2.27%)	14/44 (31.82%)
	Staphylococcus Epidermidis	0(0%)	5(100%)	5(11.36%)	
	Staphylococcus Haemolyticus	2(50.0%)	2(50.0%)	4(9.10%)	
	Staphylococcus Aureus	1(50.0%)	1(50.0%)	2(4.54%)	
	Enterococcus Faecalis	0(0%)	2(100%)	2(4.54%)	
	α-Streptococcus	0(0%)	1(100%)	1(2.27%)	
	Yeasts	0(0%)	1(100%)	1(2.27%)	
Fungus	Monilia albican	1(100%)	0(0%)	1(2.27%)	2/44 (4.54%)
	/	0(0%)	2(100%)	2(4.54%)	2/44 (4.54%)
Unclear	/	0(0%)	2(100%)	2(4.54%)	44 (100%)
Total	/	13	27	44	100%

The Distribution of microorganism in different infection sites

The distribution of microorganism from incision sites, intracranial infection sites and others for type-I and type-II incision was shown in Table 3. There were 5 gram positive bacteria (71.4%) and 2 gram-negative bacteria (28.6%) causing incision infection; there were 5 gram-positive bacteria (50.0%) and 5 gram-negative bacteria (50.0%) causing intracranial infection; and 4 gram-positive bacteria (17.4%) and 19 gram-negative bacteria (82.6%) causing other sites of infection. Infections of other sites were involved in lung, urinary tract and blood stream.

Table 3: The Distribution state of microorganism in different sites.

Species	Incision Infection		Intracranial Infection		Other Sites Infection	
	I incision surgery	II incision surgery	I incision surgery	II incision surgery	I incision surgery	II incision surgery
G ⁺	Staphylococcus Haemolyticus 2	Staphylococcus epideRmidis 3	Staphylococcus aureus 1	Staphylococcus epidermidis 1	/	Staphylococcus Haemolyticus 2
				α-Streptococcus 1		Staphylococcus Epidermidis 1
				Staphylococcus aureus 1		Staphylococcus faecalis 1
				Enterococcus faecalis 1		Stenotrophomonas maltophilia 1
				Stenotrophomonas maltophilia 1		Klebsiella pnenmoniae 4
				Klebsiella pneumonia 1		Salmonella 3
				Acinetobacter baumannii 1		P.Aeruginosa 3
G ⁻	Bacillusmacerans Schardinger 1	Bacillusmacerans Schardinger 1	/	Acinetobacter baumannii 1	/	Klebsiella pnenmoniae 1
				Escherichia co1i 1		Stenotrophomonas maltophilia 2
				Bacillusmacerans Schardinger 1		Bacillus mirabilis 1
				Bacillusmacerans Schardinger 1		Bacillus mirabilis 1
Total	3	4	1	9	9	14

Drug Susceptibility

The sensitive gram-positive and gram-negative bacteria to antibacterial agents were respectively shown in Table 4 and Table 5.

Antibacterial Agents for Prevention

Utilization rate of antibacterial agents for prophylaxis: There were 51 patients with nosocomial infection, 18 patients of which were with type-I incision, and 13 cases (72.2%) prophylactically used antibacterial agents. There were 33 patients were with type-II incision, of which 27 cases (81.8%) prophylactically used

antibacterial agents.

Table 4: Sensitivity of gram-positive bacteria to commonly-used antibacterial agents.

Antibacterials	Staphylococcus epidermidis (n=5)			Staphylococcus haemolyticus (n=4)			Staphylococcus aureus (n=2)			Enterococcus faecalis (n=2)		
	detect	sensitive	sensitivity	detect	sensitive	sensitivity	detect	sensitive	sensitivity	detect	sensitive	sensitivity
Ritampin	5	5	100%	4	4	100%	2	1	50.00%	2	0	0%
Vancocmycin	5	5	100%	4	4	100%	2	2	100%	2	2	100%
clindamycin	5	3	60.00%	3	0	0%	2	0	0%	/	/	/
linezolid	5	4	80.00%	4	4	100%	2	2	100%	2	2	100%
Gentamicin	5	1	20.00%	3	1	33.33%	2	0	0%	2	1	50.00%
Ciprofloxacin	5	4	80.00%	3	0	0%	2	1	50.00%	2	2	100%
Oxacillin	5	0	0%	3	0	0%	2	1	50.00%	/	/	/
Erythromycin	5	0	0%	3	0	0%	2	0	0%	1	0	0%
Penicillin	3	0	0%	3	0	0%	2	0	0%	2	2	100%

Timing of Prophylactic Antibacterial Administration: Timing of antibacterial agent's administration was shown in Table 6.

Redose and prophylactic duration of antibacterial agents: Among the 51 patients being investigated, 13 patients had more than 3h of type-I incision operation duration while 12 of them were not redosed with antibacterial agent during the operation (92.31%); There were 23 patients having more than 3h of type-II incision operation duration while 21 of them were not redosed with antibacterial agent. (91.30%).

The prophylactic duration of antibacterial agents in 13 patients with type-I incision was 1.92±1.55 days. There were 6 patients (46.2%) who used antibacterial for more than 24h. The prophylactic duration of antibacterial agents for 27 patients with type-II incision was 1.59±1.58 days. There were 7 patients (25.9%) who used antibacterial agents for more than 24h.

Frequency and dosage of Antibacterial Usage: A total of 6 antibacterial agents as prophylaxis were used. The frequency of usage and dosage of these agents were shown in Table 7. Though gentamicin sulfate was applied in neurosurgery, it was often used in intrathecal injection with lumbar puncture. So its Drug Utilization Index (DUI) was not calculated. DUI of another five antibacterial agents was less than 1.

Table 5: Sensitivity of gram-negative bacteria to commonly-used antibacterial agents.

Antibacterials	Klebsiella pnenmoniae (n=7)			Escherichia co1i (n=5)			P.Aeruginosa (n=3)			Salmonella (n=3)			Stenotrophomonas maltophilia (n=3)		
	detect	sensitive	sensitivity	detect	sensitive	sensitivity	detect	sensitive	sensitivity	detect	sensitive	sensitivity	detect	sensitive	sensitivity
Cefazidime	7	7	100%	5	2	40.00%	3	2	66.67%	3	3	100%	/	/	/
Pentanydrate Cefepime	7	7	100%	5	2	40.00%	2	1	50.00%	3	3	100%	/	/	/
Levofloxacin	7	7	100%	5	4	80.00%	2	1	50.00%	3	3	100%	3	3	100%
Impipenem	7	7	100%	5	5	100%	3	2	66.70%	3	3	100%	/	/	/
Meropenem	7	7	100%	5	5	100%	3	2	66.70%	3	3	100%	/	/	/
Piperacillin and Tazobactam	7	7	100%	3	2	66.70%	3	3	100%	3	3	100%	/	/	/
Amoxicillin/Clavulanic acid	6	5	83.33%	4	2	50.00%	/	/	/	/	/	/	/	/	/
Cefotaxime Sodium	6	6	100%	5	1	20.00%	/	/	/	3	3	100%	/	/	/
Gentamicin	6	5	83.33%	5	1	20.00%	3	3	100%	3	3	100%	/	/	/
Ampicillin and Sulbactam	5	5	100%	5	0	0%	/	/	/	3	3	100%	/	/	/

Discussion

The Indications of Prophylaxis

Type-I incision is in sterile operation for aseptic visceral organs. Thus generally it does not need to prophylactically apply antibacterial agents [3]. The exceptions for this rule are as follows: long operation duration, large operation range, and involvement of important visceral organs (such as heart and head), involvement of foreign body implantation (such as artificial heart valve) and high-risk factors for patients inducing infection (such as advanced age, immunodeficiency, malnutrition and diabetes). Neurosurgery gets involved in important organs, such as head, etc. Thus, any infection related to the surgery may cause serious consequences. Among the 13 patients who was given antibacterial agents with type-I incision in this investigation, there were different infectious risk factors for patients, such as long-term bedrest, immunodeficiency and other underlying diseases. In addition, the level of C-reactive protein

was significantly increased when infection occurred [4]. Proper prophylactic use of antimicrobial agents could control the rate of surgical site infection (SSI) and reduce the potential nosocomial infection rate [5]. As a result, these 13 patients had the indication of prophylactic use of antibacterial agents.

Type-II incision is sterile-contaminated operation, usually with a large amount of flora in the operation sites. Generally preventive administration of antibacterial agents is required in this case. Among the 33 infection patients with type-II incision operation, 27 patients were given prophylactic antibacterial agents, while 6 patients were not given, of which 5 patients got intracranial infection and 1 patient got urinary tract infection.

Therefore, it is suggested that patients with type-I incision operation should be evaluated to determine whether to apply prophylactic antibacterial agents. Patients with type-II incision operation should be applied prophylactic antibacterial agents.

Administration timing of Prophylactic Antibacterial Agents

The timing for medication administration should be within a short period of time before the incision [5]. Generally, prophylactic antibacterial agents were administered through intravenous drip. It is the best way to be administered 0.5-1h before the skin and mucosa being incised, ensuring that drug concentration of local operative exposing tissues is enough to kill infectious bacteria during the operative process. Antibacterial agents should be infused for a long time, such as fluoroquinolone or vancomycin, and should be given 1-2h before operation.

In this study (Table 6), patients using prophylactic antibacterial agents with type-I incision were administered mainly within 24h after operation (11 patients, 84.6%) and 2h before operation (8 patients, 61.5%). In patients with type-II incision, patients were given prophylactic antibacterial agents mainly 2h before operation (16 patients, 59.3%) and within 24h after operation (14 patients, 51.9%). Xue Yuehua [6] et al. reported 386 patients with type-I incision neurosurgery, of which a total of 84 patients was applied prophylactic antibacterial agents. There were 5 patients got incision-site infection, in 23 patients who was not given antibacterial agents before operation or accepted 2h earlier before operation. The infection incidence was 21.74%; while, only 3 patients got infection, in 61 patients who were given antibacterial agents 2h before operations, and the infection incidence was 4.92%. As a result, the timing of administering prophylactic antibacterial agents could effectively reduce infection incidence.

Table 6: Timing of antibacterial agent's administration for different types of incision.

Administration timing	Rate	
	Type I incision (13)	Type II incision (27)
>2h before operation	8/13 (61.5%)	16/27(59.3%)
1~2h before operation	0/13 (0%)	3/27 (11.1%)
0.5~1h before operation	0/13 (0%)	1/27 (3.7%)
< 0.5h before operation	0/13 (0%)	2/27 (7.4%)
During operation	2/13 (15.4%)	4/27 (14.8%)
Within 24 hours after operation	11/13(84.6%)	14/27 (51.9%)

There is no bacterial contamination before operation. So the administration of antibacterial agents 2h earlier before operation or 24h before operation is useless. Even it may increase adverse effects or screens out drug-resistant strain in advance [7]. Additionally, bacterial contamination only takes place during the operation period. The administration of antibacterial agents after operation neither effectively prevent infection from

operation sites, nor kill bacteria that had invaded and multiplied in those tissues. Therefore, it is not necessary to continuously use antibacterial agents after operation. It is critical to take advantage of the best timing to provide medication administrating, so as to let them play the maximum antibacterial roles. Advance or delay can't reach the favourable prophylactic effects. This result suggests the administration timing of preventive antibacterial should be adjusted.

The Redose and Prophylactic Duration of Antibacterial agents

According to the Guiding Principle of Clinical Application for Antibacterial Agents, type-I incision operation with the short operation duration (<2h) needs one dose of preoperative antibacterial agent. If operation duration exceeds 3h or is more than twice of the half-life of the antibacterial agent, or the amount of bleeding exceeds 1500 ml during the operation, antibacterial agents should be given a second dose during the operation. In our investigation, in those patients with operation duration for more than 3h, regardless type-I and type-II incision, only 1 patient (7.69%) and 2 patients (8.70%) were redosed with the antibacterial agent. For patients whose operation time exceeding 3h but was not redosed with the antibacterial agent, the prophylactic effect was not as good as expected, possibly because the duration of the effective drug concentration did not fully cover the whole operation process. Consistent with our results, it has been reported that the lack of prophylactic redose has been reported as a significant risk factor for SSI in various surgical fields [4].

Furthermore, the duration of prophylactic antibacterial agents should not apply for more than 24h in sterile operation and sterile-contaminated incision operation. Excessive delay of antibacterial agents use cannot improve prophylactic effects in the investigation, there were 6 patients (46.2%) with type-I incision and 7 patients (25.9%) with type-II incision had more than 24h use of antibacterial agents use and similar results showed that usage duration of delaying antibacterial agents after operation couldn't reduce infection incidence [8-9]. It is because excessive long duration of antibiotic use may easily result in dysbacteriosis and secondary infection. Meanwhile, it has a close relation with bacteria resistance and side effect [10-11]. Therefore, it is necessary to strictly control the duration of antibiotic prophylaxis to make the best preventive role of them.

Selection of Antibacterial Agents

Antibiotic prophylaxis in perioperative period mainly prevents SSI [12]. Neurosurgery site infection usually occurs in incision or in-depth organs or lacuna (such as incision infection, brain abscess and meningitis) during perioperative period.

Therefore, there are two principles for the selection of antimicrobial agents: First it can cover pathogens. Second, it can penetrate the blood-brain barrier. According to the situation of infection bacteria (Table 3), Type-I SSI bacteria are mainly gram-positive bacteria (75.0%, 3/4), especially Hemolysis Staphylococcus. Therefore, we should choose strong antibacterial agents against gram-positive bacteria for Type-I incision SSI prevention. In this research, the most frequently used agent for Type-I incision surgical prophylaxis was mezlocillin/sulbatam and clindamycin injection (Table 7). The mezlocillin/sulbatam is a broad-spectrum antimicrobial agent. It is not reasonable to choose this agent according to the results of this study. According to Table 4, the sensitivity of clindamycin to gram-positive bacteria

detected was generally low, thus, it was not reasonable to be chosen. Penicillin and the first-generation of cephalosporin are usually recommended for the gram-positive bacteria, but according to Table 4, penicillin is highly resistant to gram-positive bacteria (except for *Enterococcus faecalis*). Therefore, according to this study results of antibacterial spectrum and drug susceptibility (Table 4), the first generation of cephalosporin, such as cefazolin, is recommended to be used for prophylactic use of antibacterial agents for Type-I surgical incision. The ratio of gram-positive bacteria in SSI with Type-II incision (53.8%, 7/13) was slightly higher than that of the gram-negative bacteria (46.2%, 6/13). Therefore, for patients with Type-II incision, we should choose broad-spectrum antibacterial agents to prevent infection. The most commonly used prophylactic agents were piperacillin/sulbatam and clindamycin injection. According to the antibacterial spectrum and drug resistance rate, the second-generation cephalosporin was recommended, such as cefuroxime. In addition, post-neurosurgical meningitis caused by gram-negative bacteria has been increasingly reported in recent years [13]. Due to the limited number of cases in this study, whether the piperacillin/sulbatam can be selected need to be further explored.

According to the latest investigation of the distribution of pathogen (Table 3), 5 strains of gram-positive bacteria (71.4%) and 2 strains of gram-negative bacteria (28.6%) were found in the incision infection, while 5 strains of gram-positive bacteria (50.0%) and 5 strains of gram-negative bacteria (50.0%) were found in intracranial infection. This result is distinguished from most of the previous reported results, whose data were not generally subdivided into incision infection and intracranial infection. It has been shown in other reports that SSI was mainly caused by gram-positive bacteria [14]. Therefore, this new result is an especial important reference for choosing the appropriate antimicrobial agents in the prevention and treatment of postoperative SSI in neurosurgery patients.

Gram-negative pathogens were seen more frequently from other infection sites, such as lung, urinary tract and blood (Table 3). So the third-generation cephalosporin was recommended.

This study (Table 4 and Table 5) showed most of gram-positive bacteria were susceptible to vancomycin; Most of gram-negative bacteria were susceptible to meropenem. Therefore, in severe cases, vancomycin and meropenem can be chosen based on pathogens susceptibility for postoperative SSI in neurosurgery patients.

Prophylactic Antibacterial Dosage

DUI is an indicator to evaluate whether drugs are abused. The six prophylactic antibacterial agents used in this investigation were strictly in accordance with the drug instruction, and the drug utilization indices were all less than 1, indicating all of the doses were reasonable.

Summary

Postoperative infection greatly increased the patient's financial burden, prolonged the hospitalization duration and resulted in unnecessary use of health resources [14].

Our current investigation showed that prophylactic antibacterial agent selection, administration timing and prophylactic duration during perioperative period of oncological neurosurgery should be adjusted to reduce nosocomial

infection. Therefore, excluding the factors of surgery itself, environment and so on, it is necessary to pay attention to the application of antibacterial agents in the perioperative period of neurosurgery.

The factors for the use of antibacterial agents that need to take into consideration are as follows

Evaluating whether there is the indication for prophylactic use of antibacterial agents, strictly following the optimal timing of antibacterial administration and the schedule, taking into consideration of the type of incision, the latest epidemiological investigation of the pathogens, drug sensitivity data and pharmacokinetic/pharmacodynamic characteristics of the medications, so as to choose medications with more effective profile and less adverse reaction, better tissue penetration, cheaper prices, in order to reduce postoperative infection risk and improve the patient prognosis [15].

Especially our data of the distribution of the pathogens were divided into two subgroups, incision infection and intracranial infection groups, both of which were together counted as Surgical Site Infection (SSI) before. Our statistical strategy will provide more details of the nosocomial infection and be an important reference for clinical application of antibacterial agents.

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