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Flora characteristics and risk factors of lower respiratory tract infections in patients with severe craniocerebral trauma in the intensive care unit

Vlastnosti mikroflóry a rizikové faktory infekcí dolních cest dýchacích u pacientů se závažným kraniocerebrálním poraněním na jednotce intenzivní péče

Abstract

Aim: The aim of the study was to explore the flora characteristics and risk factors of lower respiratory tract infections in patients with severe craniocerebral trauma in intensive care unit. *Patients and methods:* The clinical data of 457 eligible patients hospitalized from August 2015 to March 2020 were collected, and incidence rate of infections, pathogen distribution and drug sensitivity test results were recorded. Related risk factors were analyzed. *Results:* Out of the 457 patients, 150 had lower respiratory tract infections. A total of 78 (52.00%) strains of Gram-positive bacteria, 65 (43.33%) strains of Gram-negative bacteria, and 7 (4.67%) strains of fungi were isolated through sputum culture. Multi-drug resistant and fully resistant strains in main Gram-negative bacteria had higher detection rates. Gram-positive bacteria were 100% sensitive to vancomycin and teicoplanin and only *Staphylococcus haemolyticus* was fully resistant to erythromycin. Age, duration of coma, tracheal intubation or incision, use of ventilators, and use of antibiotics were independent risk factors ($P < 0.05$). *Conclusion:* The main pathogens for lower respiratory tract infections in patients with severe craniocerebral trauma in intensive care unit have extensive drug resistance and high resistance rates. It is necessary to ensure aseptic operations, strictly prevent cross infections, and improve the immune function of patients, thereby improving the therapeutic effect.

Souhrn

Cíl: Cílem této studie bylo prozkoumat vlastnosti mikroflóry a rizikové faktory infekcí dolních cest dýchacích u pacientů se závažným kraniocerebrálním poraněním na jednotce intenzivní péče. *Soubor pacientů a metody:* Byla shromážděna klinická data 457 vhodných pacientů hospitalizovaných od srpna 2015 do března 2020 a byly zaznamenány výskyt infekcí, distribuce patogenů a výsledky testů citlivosti na antimikrobiální léčiva. Byly analyzovány příslušné rizikové faktory. *Výsledky:* Z celkového počtu 457 mělo 150 pacientů infekce dolních cest dýchacích. Po kultivaci vzorků sputa bylo izolováno celkem 78 (52,00 %) kmenů grampozitivních bakterií, 65 (43,33 %) kmenů gramnegativních bakterií a 7 (4,67 %) kmenů kvasinek a plísní. Mezi nejčastějšími gramnegativními bakteriemi bylo zachyceno více multirezistentních nebo plně rezistentních kmenů. Grampozitivní bakterie vykazovaly 100% citlivost vůči vankomycinu and teikoplaninu a pouze *Staphylococcus haemolyticus* byl plně rezistentní vůči erythromycinu. Mezi nezávislé rizikové faktory patřily věk, doba trvání kómatu, tracheální intubace nebo incize, použití umělé plicní ventilace a podávání antibiotik ($p < 0,05$). *Závěr:* Nejčastější patogeny vyvolávající infekce dolních cest dýchacích u pacientů se závažným kraniocerebrálním poraněním na jednotce intenzivní péče vykazují rezistenci na široké spektrum antimikrobiálních léčiv a vysokou míru rezistence. Je nutné zajistit operace v aseptickém prostředí, striktně zabránit zkříženým infekcím a zlepšit imunitní funkce pacientů, čímž dojde ke zlepšení terapeutického účinku.

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Introduction

Severe craniocerebral trauma, a common critical neurosurgical disease in the intensive care unit (ICU), progresses rapidly, and it is extremely likely to cause the death of patients if not treated promptly. Clinically, the common invasive therapies include tracheal intubation or incision and use of ventilators. However, patients in the ICU are easily afflicted with bacterial infections, the most common of which are lower respiratory tract infections due to the critical disease condition-caused decline in immunity together with invasive treatments and long-term use of high-dose broad-spectrum antibacterial drugs, diuretics and hormones [1]. Notably, bacterial drug resistance has become increasingly prominent due to massive use of antibacterial drugs [2]. In recent years, lower respiratory tract infections are often considered as important risk factors for the death of patients with severe craniocerebral trauma [3]. Therefore, it is of great significance to explore the pathogen distribution, clinical characteristics, and risk factors of lower respiratory tract infections in patients with severe craniocerebral trauma in the ICU for the prevention and control of bacterial infections and the improvement of rescuing success rate and survival quality of critical patients.

The aim of this study was to investigate the flora characteristics and risk factors of lower respiratory tract infections, and to provide bases for the clinical prevention, control and treatment of lower respiratory tract infections in patients with severe craniocerebral infections in the ICU.

Patients and methods

Baseline clinical data

In our retrospective study, a total of 457 patients with severe craniocerebral trauma hospitalized in the ICU of our hospital from August 2015 to March 2020 were enrolled as subjects. Inclusion criteria were: Glasgow Coma Scale score of 3–8 points; availability of complete clinical data and informed consent voluntarily signed by relatives. Exclusion criteria were: history of combined injury, multiple injuries and craniocerebral trauma as confirmed by physical examination and head CT; history of acute and chronic inflammation, diabetes, abnormal renal function, pulmonary diseases and pulmonary contusion before trauma; symptoms and signs of lower respiratory tract infections within 48 h after admission; food consumption within 4–6 h prior to admission; the use of glucocorticoid, sugar-containing drugs, anticoagulants or the drugs affecting fibrinolytic activity before admission.

Among the 457 patients with severe craniocerebral trauma, 318 were males, and they were 30–78 years old with a mean of 43.52 ± 5.61 years. There were 99 cases of injuries due to falling on the ground, 175 cases of high fall injuries, 61 cases of blunt trauma injuries, 122 cases of traffic accident injuries, 96 cases of brain-stem injuries, 61 cases of epidural hematoma, 128 cases of subdural hemorrhage, 82 cases of subarachnoid hemorrhage, and 90 cases of intracerebral hematoma.

Diagnostic criteria for lower respiratory tract infection

According to the Guidelines for the Management of Adult Lower Respiratory Tract Infections [4], patients had such clinical manifestations as cough, cough producing purulent sputum and pulmonary moist rales, and any of the following conditions: body temperature > 37.5 °C; inflammatory infiltrative lesions in the lungs as shown in chest imaging examination; and positive bronchial secretion culture results or a white blood cell count > 12.0×109/mL as indicated in laboratory tests.

Isolation and identification of bacteria

Clinical medical staff collected specimens with reference to the National Guide to Clinical Laboratory Procedures (4th Ed.) [5]. First, sputum was collected into an aseptic container using a closed endotracheal tube and timely sent to the Microbiological Laboratory for pathogenic detection. The specimens sent for detection were considered to meet quality control criteria, if it was microscopically observed that the ratio of multinuclear leukocytes to squamous epithelial cells in the sputum specimens was lower than 2.5, or the count of multinuclear leukocytes was not lower than 25 and that of squamous epithelial cells was not higher than 10 in each low-power field of view. The sticky sputum needed to be trypsinized first. Then, the sputum specimens were inoculated onto a blood agar plate, a chocolate agar plate or a MacConkey agar plate on an aseptic operator's station and cultured in an incubator at 37 °C for 24 h. Following growth of bacterial strains, a single bacterial colony was picked up for Gram staining. Based on the staining results, the types of bacteria were identified using the VITEK 2 Compact automatic microorganism identification and drug sensitivity analyzer (BioMérieux, Marcy-l'Étoile, France) and its equipped reagents strictly in accordance with operation specifications.

Drug susceptibility test

Routine drug susceptibility test was conducted for the isolated and cultured pathogens using the above-mentioned automatic microorganism identification and drug sensitivity analyzer and its equipped drug sensitivity cards, and the test was repeated 3 times to ensure the accuracy of the results. *Staphylococcus aureus* (ATCC25923), *Pseudomonas aeruginosa* (ATCC27853), *Acinetobacter baumannii* (ATCC19606), *Escherichia coli* (ATCC25922), *Enterococcus faecalis* (ATCC29212), *Klebsiella pneumoniae* (ATCC700603) and *Candida albicans* (ATCC 14053) (the National Center for Clinical Laboratories) were taken as quality control strains. Finally, laboratory test results were assessed according to the criteria formulated by the USA Clinical & Laboratory Standards Institute [6].

Statistical analysis

All data were statistically analyzed using SPSS 16.0 software (IBM, Armonk, NY, USA). The numerical data were expressed as case (%) and subjected to the Chi-square test. The quantitative data were represented as mean ± standard deviation and subjected to the independent t-test. The risk factors for the occurrence of lower respiratory tract infections were analyzed by using the logistic regression model. $P < 0.05$ was considered statistically significant.

Results

Lower respiratory tract infection rate and distribution of pathogenic bacteria

There were 150 cases of lower respiratory tract infections among the 457 enrolled patients with severe craniocerebral trauma, and the infection rate was 32.85%. A total of 78 (52.00%) strains of Gram-negative bacteria, dominated by *P. aeruginosa, A. baumannii* and *K. pneumoniae,* 65 (43.33%) strains of Gram-positive bacteria, including *S. aureus, S. haemolyticus* and *E. faecalis,* and 7 (4.67%) strains of fungi, including *C. albicans* were isolated and identified through the sputum culture in the 150 cases (Tab. 1).

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Drug susceptibility of main Gram-negative bacteria

Gram-negative bacteria, among the top 3 in terms of composition proportion, were subjected to a drug sensitivity test, and it was found that multi-drug resistant strains and fully resistant strains had higher detection rates. *P. aeruginosa* exhibited 100% resistance to ceftriaxone, ampicillin, ampicillin/sulbactam, and sulfamethoxazole/trimethoprim, 96% resistance to cefazolin, and 88% resistance to cefotetan, whereas it was 100% sensitive to tobramycin, amikacin, and ertapenem and < 20% resistant to other antimicrobial agents. *A. baumannii* was 100% resistant to cefazolin, cefotetan, amikacin and ampicillin and 100% sensitive to ertapenem, with varying rates of resistance to other antibiotics. *K. pneumoniae* was fully resistant only to ampicillin, with no resistance to tobramycin, amikacin and ertapenem and different degrees of resistance to other antibacterial drugs (Tab. 2).

Tab. 1. Pathogenic bacteria isolated from patients with lower respiratory tract infections.

Pathogenic bacteria	Stain No.	Proportion (%)
Gram-negative bacteria	78	52.00
P. aeruginosa	25	16.67
A. baumannii	21	14.00
K. pneumoniae	16	10.67
E. coli	7	4.67
Enterobacter cloacae	6	4.00
Stenotrophomonas maltophilia	3	2.00
Gram-positive bacteria	65	43.33
S. aureus	24	16.00
S. haemolyticus	21	14.00
E. faecalis	20	13.33
Fungi	7	4.67
C. albicans	4	2.67
Saccharomyces albicans	3	2.00

Drug susceptibility of Gram-positive bacteria

Based on the drug sensitivity test results of Gram-positive bacteria, *S. aureus* showed the highest rate of resistance to penicillin G (91.67%) and 100% sensitivity to vancomycin, teicoplanin, and linezolid. *S. haemolyticus* was fully resistant to erythromycin, 95.24% resistant to penicillin G, and 90.48% resistant to gentamicin, with 100% sensitivity to vancomycin, teicoplanin and linezolid. The resistance rate of E. faecalis to penicillin G was 95%, followed by 90% resistance to oxacillin, 55% resistance to levofloxacin, and < 50% resistance to other antibiotics, and it was 100% sensitive to vancomycin and teicoplanin (Tab. 3).

Tab. 2. Drug susceptibility of main Gram-negative bacteria.

Drug	*P. aeruginosa* (N = 25)		*A. baumannii* (N = 21)		*K. pneumoniae* (N = 16)	
	strain No. (%)	resistance rate	strain No. (%)	resistance rate	strain No. (%)	resistance rate
ceftriaxone	25	100.00	14	66.67	7	43.75
cefazolin	24	96.00	21	100.00	12	75.00
cefotetan	22	88.00	21	100.00	2	12.50
ceftazidime	4	16.00	11	52.38	5	31.25
cefepime	2	8.00	18	85.71	4	25.00
gentamicin	1	4.00	12	57.14	1	6.25
tobramycin	0	0.00	12	57.14	0	0.00
amikacin	0	0.00	21	100.00	0	0.00
ciprofloxacin	3	10.12	13	61.90	3	18.75
levofloxacin	2	8.00	9	42.86	3	18.75
ampicillin	25	100.00	21	100.00	16	100.00
ampicillin/sulbactam	25	100.00	16	76.19	6	37.50
piperacillin/tazobactam	3	10.12	7	33.33	2	12.50
imipenem	1	4.00	2	9.52	3	18.75
ertapenem	0	0.00	0	0.00	0	0.00

N – number

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Tab. 3. Drug susceptibility of Gram-positive bacteria.

Drug	*S. aureus* (N = 24)		*S. haemolyticus* (N = 21)		*E. faecalis* (N = 20)	
	strain No. (%)	resistance rate	strain No. (%)	resistance rate	strain No. (%)	resistance rate
erythromycin	18	75.00	21	100.00	5	25.00
rifampin	8	33.33	6	28.57	3	15.00
penicillin G	22	91.67	20	95.24	19	95.00
oxacillin	19	79.17	17	80.95	18	90.00
cefazolin	4	16.67	4	19.05	3	15.00
levofloxacin	13	54.17	11	52.38	11	55.00
gentamicin	14	58.33	19	90.48	2	10.00
clindamycin	6	25.00	7	33.33	6	30.00
sulfamethoxazole/trimethoprim	1	4.17	5	23.81	4	20.00
vancomycin	0	0.00	0	0.00	0	0.00
teicoplanin	0	0.00	0	0.00	0	0.00
linezolid	0	0.00	0	0.00	1	5.00

N – number

Univariate analysis results of factors affecting lower respiratory tract infections

According to the presence or absence of lower respiratory tract infections, patients with severe craniocerebral trauma were allocated into the infection group and non-infection group, and it was discovered that the two groups of patients were not statistically significantly different regarding sex, causes of injuries, injured site, smoking history, nasal feeding, sputum aspiration and indwelling of venous catheters ($P > 0.05$). Compared with the non-infection group, the infection group patients exhibited a higher age, longer duration of coma, and more cases of tracheal intubation or incision, use of ventilators and use of antibiotics, displaying statistically significant differences ($P < 0.05$) (Tab. 4).

Multivariate logistic regression analysis results of factors affecting lower respiratory tract infections

Logistic regression analysis was conducted on the statistically significant variables in the univariate analysis as independent variables and the development of lower respiratory tract infections as the dependent variable. According to the results, patients age, duration of coma, tracheal intubation or incision, use of ventilators and use of antibiotics were the risk factors for the occurrence of lower respiratory tract infections in patients with severe craniocerebral trauma in the ICU ($P < 0.05$) (Tab. 5).

Discussion

Since patients with severe craniocerebral trauma in the ICU are seriously injured and suffer from complications such as shock, coma, combined chest and abdominal injuries and multiple fractures, their immune function is compromised. Besides, clinical rescue approaches such as invasive operations and massive use of antibiotics and immunosuppressors are extremely likely to induce in-hospital infections in patients, of which the most common and severe are lower respiratory tract infections. These mainly affect the important organs maintaining the ventilation of human body, including the trachea, bronchi and lungs, so they can aggravate craniocerebral trauma and worsen the prognosis.

In the present study, among the 457 enrollees with severe craniocerebral infections, 150 had lower respiratory tract infections, with an infection rate of 32.85%. It was found through the culture of sputum specimens that Gram-negative bacteria were the major pathogens causing lower respiratory tract infections in patients with severe craniocerebral trauma, consistent with numerous literature reports worldwide [7]. Additionally, many Gram-positive bacteria and few fungi were observed, which suggests the complex distribution of the pathogens responsible for lower respiratory tract infections in the Infection ICU. Among Gram-negative bacteria, *P. aeruginosa, A. baumannii* and *K. pneumoniae* were among the top 3 in terms of the composition proportion, the detected Gram-positive bacteria included *S. aureus, S. haemolyticus,* and *E. faecalis,* and *C. albicans* was the detected fungus. The drug sensitivity test results revealed that there were more multi-drug resistant strains and fully resistant strains in the major Gram-positive bacteria, whereas Gram-positive bacteria were 100% sensitive to vancomycin and teicoplanin, of which only *S. haemolyticus* was fully resistant to erythromycin. Moreover, different pathogens exhibited relatively extensive drug resistance, and their resistance to the same antibiotic varied to a certain extent. The distribution and drug resistance of pathogens in lower respiratory tract infections were not completely consistent with previous literature [8]. It is thus inferred that dominant resistant strains were altered due to the smaller sample size in the present study, differences in the antibiotic types and doses used in regions or hospitals, and the drug resistance mechanisms of different flora. Therefore, antibiotics to which pathogens are sensitive should be chosen carefully and properly used based on the results of the pathogen test and drug susceptibility test in the clinical treatment of lower respiratory tract infections in patients with severe craniocerebral trauma in the ICU.

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Tab. 4. Univariate analysis results of factors affecting lower respiratory tract infections.

Factor	Infection group (N = 150)	Non-infection group (N = 307)	t/χ^2	P
age (year, $\bar{x} \pm SD$)	45.63 ± 5.82	37.48 ± 4.59	15.017	< 0.001
sex (case, %)			0.007	0.935
male	104	214		
female	46	93		
cause for injury			5.887	0.117
fall injury	30	69		
fall injury from high place	49	126		
blow injury	21	40		
car accident injury	50	72		
injured part			3.264	0.083
brain-stem injury	30	66		
epidural hematoma	22	39		
subdural hemorrhage	43	85		
subarachnoid hemorrhage	26	56		
intracerebral hematoma	29	61		
smoking duration (years, $\bar{x} \pm SD$)	28.73 ± 9.64	29.16 ± 10.07	0.435	0.664
coma duration (days, $\bar{x} \pm SD$)	10.25 ± 1.48	5.37 ± 0.62	49.590	< 0.001
tracheal intubation or incision			12.997	< 0.001
yes	112	176		
no	38	131		
use of ventilator			21.361	< 0.001
yes	124	188		
no	26	119		
nasal feeding			1.801	0.180
yes	83	190		
no	67	117		
sputum suction			0.049	0.826
yes	92	185		
no	58	122		
retention of venous catheter			0.004	0.950
yes	87	179		
no	63	128		
use of antibiotics			35.849	< 0.001
yes	125	168		
no	25	139		

N – number; SD - standard deviation

Invasive operations and use of antibiotics have been reported to be the risk factors for lower respiratory tract infections in patients with craniocerebral trauma-induced coma [9]. Additionally, body temperature, blood glucose, duration of coma, duration of hospital stay, indwelling time of gastric tube, tracheal incision and use of ventilators are the risk factors for lower respiratory tract infections in patients with severe craniocerebral trauma in the ICU [10]. According to the results of this study, the development of lower respiratory tract infections in patients with severe craniocerebral trauma in the ICU was closely related to patients age, duration of coma, tracheal intubation or incision, use of ventilators and use of antibiotics. This finding is consistent with the above-mentioned study reports. As age increases, the organ functions and body immunity of patients will decline together with atrophy of res-

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Tab. 5. Multivariate logistic regression analysis results of factors affecting lower respiratory tract infections.

Factor	β	SE	Wald χ^2	P	OR	95% CI
age	0.837	0.562	2.405	0.021	2.573	1.218~3.095
coma duration	0.629	0.741	1.836	0.002	3.485	2.594~4.671
tracheal intubation or incision	1.526	0.629	3.278	0.014	4.139	3.067~5.842
use of ventilator	2.431	0.874	4.052	0.005	5.207	2.436~6.279
use of antibiotics	0.794	0.935	3.649	0.013	4.725	3.398~5.143

Age: ≥ 60 years old = 1, < 60 years old = 0; coma duration: ≥ 7 days = 1, < 7 days = 0; tracheal intubation or incision: yes = 1, no = 0; use of ventilator: yes = 1, no = 0; use of antibiotics: yes = 1, no = 0.
CI – confidence interval; OR – odds ratio; SE – standard error

piratory mucosa and decreased ciliary motility, which weakens cough, expectoration and other normal physiological functions. Moreover, patients with severe craniocerebral trauma are in a coma, so the secretions in the lower respiratory tract fail to be normally discharged, thereby triggering lower airway obstruction. Ultimately, infections are induced due to retention of massive inhaled pathogens in the lower respiratory tract [11]. Additionally, coma greatly weakens the swallowing function of patients with severe craniocerebral trauma, and intracranial hypertension is extremely likely to induce vomiting, thereby resulting in accidental aspiration. Gastric contents reversely flow into the respiratory tract and further worsen its obstruction and mucosal damage, thus heightening the risk of infections [12]. Tracheal intubation or incision for opening the airway in patients with severe craniocerebral trauma seriously destroys the filtration, humidification and thermoregulation functions of the respiratory tract and other natural protective barriers. The mucosal blood flow is altered since the tracheal wall continues to be compressed by the tube, and the high-pressure air bag blocks the blood between tracheal cartilages and impairs the defense function of the respiratory system. Besides, frequent negative-pressure suction can also damage respiratory mucosa, and pathogens in the air and below the pharynx adhere to the respiratory tract where they are colonized, thereby inducing infections [13]. Long-term use of ventilators can cause respiratory mucosal damage as well. In particular, the condensed water in the tube can contribute to massive multiplication of bacteria, and moving the tube or changing the positions of patients can extremely easily allow the condensate with bacteria to enter the lower respiratory tract, leading to infections. Therefore, ventilators should be strictly disinfected [14]. Additionally, long-time use of antibiotics tends to make strains drug-resistant, thereby giving rise to flora disorder, and it can suppress the normal immune response in organisms to a certain degree, ultimately inducing infections [15].

In summary, the major pathogens for lower respiratory tract infections in patients with severe craniocerebral trauma in the ICU have high drug resistance rates and extensive drug resistance, so antibiotics should be properly used for the treatment based on clinical trials to reduce bacterial resistance. Moreover, measures should be taken to ensure aseptic operations, strictly prevent cross infections, and improve the immune function of patients, thereby improving the efficacy. Based on the etiological characteristics and risk factors of lower respiratory tract infections in this study, it is recommended that the following prevention measures should be applied in patients with severe craniocerebral trauma in the ICU. The type and drug resistance of pathogens should be promptly identified for many times, and targeted medication should be initiated based on the test results if the conventional empirical treatments have poor efficacy. The wards need to be kept clean, and terminal disinfection should be regularly performed to strictly prevent cross infection if appropriate. Invasive operations should be completed aseptically, and patients should be cared for well. Once it is ensured that a primary disease is effectively treated, nutritional support treatment should be carried out to strengthen the immune functions of patients, especially the elderly.

Ethical aspects

The entire study was conducted in accordance with the Helsinki Declaration of 1975 (as revised in 2004 and 2008). This study was conducted upon the review and approval of the Medical Ethics Committee of Beijing Friendship Hospital, Beijing, China on August 4, 2015 (approval number: 2020 P2 065P01).

Conflict of interest

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

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