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Optimization of Antibiotic Drug Regimens to Patients with Renal Dysfunction Based on Endogenous CLcr and Commenting on Its Rationality

Abstract:Objective: To optimize the antibiotic drug regimens to patients with renal dysfun-ction based on endogenous creatinine clearance(CLcr) and to comment on its rationality. Methods: Rationality and optimizability of the antimicrobial regimens in a medical record were disscussed via the renal function based on CLcr. The original regimens which were considered to be optimized were adjusted via the renal function based on CLcr, When these adjusted regimens achieved the preset threshold of the PK/PD target index which was used to predict the efficacy of regimens, they were considered to be feasible. Results: In the elected medical record, it was found that the dosage of the original regimens was too high or the interval of administration was too short, which indicated that the original regimens could be optimized. The optimized regimens, obtained by adjustment on the original regimens via the renal function based on CLcr and according to the preset threshold of the PK/PD target index, were theoretically not only effective but also more secure. Conclusion: Based on the renal function status reflected by CLcr, the optimization and commenting of antimicrobial drug administration plan and its rationality are helpful for the development of safe, effective and reasonable individualized treatment plan for patients with renal insufficiency complicated with infection; it can serve as the theoretical guidance in clinical practice.

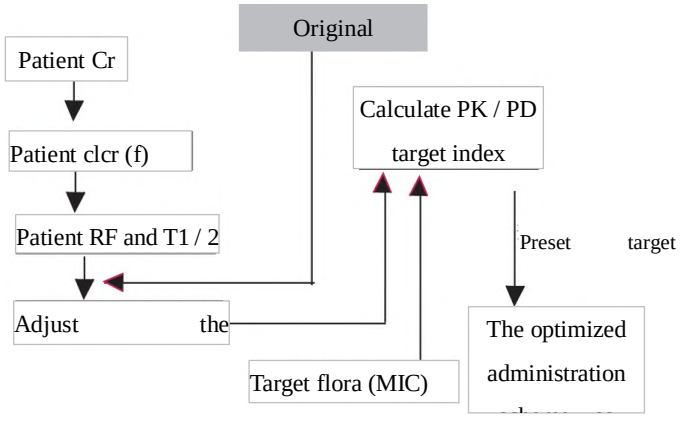
Key words: Endogenous creatinine clearance; Renal insufficiency; Infection; Antibiotics; PK/PD target index

For patients with renal insufficiency complicated with infection, the formulation of antibacterial drug administration scheme (including antibacterial drug variety, dose, administration frequency or interval, drug safety and metabolism, etc.) is often different from ordinary patients. Clinically, doctors often ignore the influence of the changes of pharmacokinetic parameters caused by patients' renal insufficiency on the formulation of drug delivery plan, and choose the empirical plan of conventional treatment. The insufficient use of empirical plan leads to treatment failure, and excessive use of drugs not only wastes drugs, but also makes the drug accumulation in patients' body, resulting in potential adverse reactions, especially the drugs excreted through the kidney and with nephrotoxicity. For patients with renal insufficiency complicated with infection, how to formulate a safe, effective and reasonable antibacterial drug administration scheme is a major problem faced by both doctors and pharmacists. As a routine test item widely carried out in clinical laboratories, creatinine has met the standardization and consistency in test methodology. Serum creatinine concentration (CR) and endogenous creatinine clearance (CLcr) have been widely used to evaluate patients' renal function. CLcr is not only a functional index reflecting drug renal excretion, but also the most valuable basis for the formulation of drug treatment plan for patients with renal insufficiency [1-2]. Therefore, taking the fixed antimicrobial drug administration scheme in a previous medical record as an example, the author optimized and commented on the administration scheme and its rationality based on the CLcr reflecting the renal function of patients, in order to provide theoretical guidance or reference for the rational formulation of antimicrobial drug administration scheme for patients with renal insufficiency complicated with infection.

1 Data and methods

1.1 Comment on the rationality of administration scheme and optimization of ideas

According to the thought optimization diagram of administration scheme, two problems need to be clarified: (1) how to get the adjusted administration scheme based on the original administration scheme according to CR or CLcr (f); (2) How to get the optimized administration scheme according to PK / PD target index. The optimization of administration scheme is shown in Figure 1.



Note: Clcr (*f*) is the renal clearance rate of drugs in renal insufficiency, RF is the renal function factor or dose adjustment factor, $t_{1/2}$ (*f*) is the elimination half-life of drugs in renal insufficiency, and MIC is the minimum inhibitory concentration

Fig. 1 Schematic diagram of drug administration scheme optimization process

1.2 Adjustment of CLcr and administration plan

1.2.1 estimation of decline degree of renal function and factor (RF) [3] because endogenous creatinine is cleared through glomerular filtration, there is a parallel relationship between CLcr and glomerular filtration rate, that is, CLcr can reflect renal clearance function. Clcr can be calculated by Cockcroft Gault formula: CLcr = ((140 age) BW) ÷ (0.818 · CR).

Note: for female patients, the above formula should be multiplied by 0.85, where age is age (years), BW is body mass (kg), and Cr is blood creatinine concentration （ μ mol/L)]。

RF not only reflects the relationship between the renal clearance rate of drugs in normal renal function and damage, but also reflects the dose adjustment relationship of drugs. The calculation formula is $RF = 1 - [fe(1 - \mathrm{CLcr}(f)\ , \mathrm{CLcr}(n))]$. Where, CLcr (*f*) is the renal clearance rate of the drug in case of renal insufficiency, CLcr (*n*) is the normal creatinine clearance rate, the normal value for adults is 100 ml / min, and *fe* is the urinary excretion rate of the prototype drug. In general, there is a relationship between the drug elimination half-life ($t_{1/2}$ (*f*)) in renal insufficiency and the drug elimination half-life ($t_{1/2}$ (n)) in normal renal function [4], that is, $t_{1/2}$ (*f*) = $t_{1/2}$ (*n*) / RF.

1.2.2 Administration plan in case of renal insufficiency. The load dose of drugs depends on the apparent distribution volume. Generally, it is not necessary to adjust in case of renal insufficiency. However, the maintenance amount depends on the clearance rate and can be calculated from the normal dosage according to RF to reduce the toxicity caused by drug accumulation. Clinically, the following methods are commonly used to adjust: (1) maintain the dose when the renal function is normal, and the administration interval is divided by RF from the administration interval when the renal function is normal; (2) Maintain the dosing interval when the renal function is normal, and the dosage of each administration is multiplied by RF from the dosage when the renal function is normal; (3) According to the half-life extension of renal insufficiency, that is, reduce the dosage of each administration and appropriately extend the administration interval.

1.3 Optimization of drug delivery scheme based on PK / PD target index

The PK / PD target index against the target flora, penicillins and cephalosporins is *f*% *t* > MIC, and its expression is:

$$f\%\ t > \mathrm{MIC} = \ln\left(\mathrm{Dose} \times f \cdot \mathrm{Vd}^{-1} \cdot \mathrm{MIC}^{-1}\right) \times t_{1/2} \times 0.693^{-1} \times \tau^{-1} \times 100\%$$[5]。

Note: in the $f\%\ t > \mathrm{MIC}$ formula is the percentage of the time when the free blood drug concentration level is higher than the minimum inhibitory concentration in a dosing interval, dose is the dose in a dosing interval (mg), f is the percentage of free drug (calculated by 1-plasma protein binding rate), VD is the apparent distribution volume (L), and is the $t_{1/2}$ elimination half-life (H), τ Is the administration interval (H).

This kind of antibiotics generally take *f*% *t* > MIC > 50%

as the target threshold to obtain better curative effect [5]. Therefore, this kind of antibiotics will optimize the administration scheme with this target threshold.

The PK / PD target index of concentration dependent antibiotics against the target flora is AUIC, and the expression is: [5].$AUIC = Dose_{0-24\ h}/(MIC \cdot CL)$

Since CL = K_{el} · VD and K_{el} = 0.693/t1/2 in the one compartment model, $AUIC = t_{1/2} \times Dose_{0-24h} / (0.693 \times MIC \times Vd)$.

Note: in the formula, AUIC is the predicted efficacy parameter (H), dose is the dose (mg) within 0 ~ 24 h, CL is the drug clearance rate (L / h), and Kel is the elimination rate constant (1 / h).

Special attention should be paid to the PK / PD of linezolid. The American Society of infectious diseases recommends that AUC0－24 h/MIC(or AUIC) and T > MIC should be used at the same time to predict its clinical efficacy. According to the report [6-7], it is considered that linezolid AUIC is between 80 ~ 120 and T > MIC is greater than 85%, which can obtain good therapeutic effect. Therefore, linezolid will take *f*% *t* > MIC > 85% and 80 < AUIC < 120 as the target threshold to obtain better curative effect, and optimize the administration scheme.

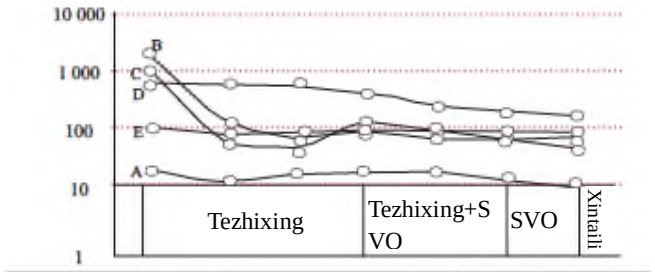
1.4 Clinical data

A patient, male, 48 years old, with a body mass of 60 kg. He was admitted to ICU on July 15, 2018 due to multiple injuries caused by being involved in the machine by the conveyor belt. At the time of admission, the basic vital signs were normal, the respiratory sounds of both lungs were thick, the edema of both lower limbs, the wound dressing was dry, the drainage was unobstructed, and the drainage fluid was light red. There was a history of diabetes mellitus, hypertension and fatty liver. The admission diagnosis was (1) multiple injuries, traumatic shock, bilateral pulmonary contusion and laceration with right hemothorax, liver contusion, pancreatic contusion, open fracture of left knee joint, fracture of left fibular head, skin and soft tissue contusion; (2) type II diabetes mellitus; (3) Renal insufficiency; (4) Hypertension; (5) Fatty liver.

On the day of admission, the patient was clinically considered for fracture, liver, spleen injury, low immunity, diabetes and renal insufficiency. It was susceptible to Enterobacteriaceae and Pseudomonas aeruginosa. Empirically, piperacillin tazobactam (terbuzine, piperacillin and tazobactam was 8: 1) 4.5 g, q8H. After the infection, blood and body temperature were decreased, but it was still high. Considering that the late effect of the drug was not ideal, samples were collected for wound secretion and blood flow culture. The results on July 25 showed that methicillin resistant Staphylococcus aureus (MRSA) was sensitive to linezolid, and its MIC was 1 mg / L by dilution method. Linezolid (SVO, 0.6 g, q12h) was added.

On July 31, piperacillin tazobactam was stopped and linezolid injection was used only. On August 3, the patient's hemogram and body temperature returned to normal, so he was transferred to the general ward and continued to fight the infection with cefazolin (neothalin, 3 G, q12h). He improved and was discharged from the hospital after 5 days.

During this period, no liver and kidney function examination was performed. See Fig. 2 for the antibiotics and laboratory test results used by the patient during hospitalization.



project	07-15	07-19	07-22	07-25	07-28	07-31	08-03
WBC(A)	18.6	11.2	14.7	16.8	16.8	11.6	9.8
AST(B)	1 769.2	137	63.1	84.6	59.5	58	67.6
ALT(C)	948.4	61.4	43.7	114.3	58.4	46.4	43.3
Cr(D)	528.4	525	488.9	361.1	222.9	183	146.3
N%(E)	88.9	72.7	80.1	84.1	84.1	84.2	76.8

Note: WBC($\times 10^9$/L); AST and ALT (U / L); Cr(μ mol/L)。

Fig. 2 antibiotics used by patients during hospitalization and laboratory test results

2 Results

2.1 Administration scheme based on CLcr adjustment

The administration scheme adjusted based on CLcr is obtained by adjusting the RF of the patient on the basis of the conventional administration scheme. According to the formula: The calculation of RF needs to obtain the CLcr of the patient and the Fe of the drug. The data of PK parameters of antibiotics in adults with normal renal function are shown in Table 1.

Table 1 Comparison of PK parameters of antibiotics in adults with normal renal function

Antibiotics	Vd (v/L·kg-1)	*f*	$t_{1/2}$ (t/h)	*fe*
Piperacillin tazobactam [8]	0.26	0.70	0.84	0.68
Linezolid [3]	0.57	0.69	5.2	0.35
Cephalazoline [3]	0.19	0.11	2.2	0.80

Based on this PK parameter, the patient's age, body mass, Cr in different periods and Fe of various antibiotics can be substituted into the formula to obtain the CLcr (*f*), RF and $t_{1/2}$ (*f*) parameter values of the patient in different periods, as shown in Table 2.

Finally, according to RF, based on the original administration scheme of each antibacterial drug, the adjusted administration scheme of each drug in different periods can be obtained, as shown in Table 3.

Table 3 shows that between 07-25-07-31 and 07-31-08-03, the adjusted dosing scheme of linezolid is relatively close, so only the adjustment scheme of 07-25-07-31 is selected for discussion when evaluating and optimizing the rationality of the adjustment scheme of linezolid.

Table 2 Comparison of CLcr (*f*), RF and $t_{1/2}$ (*f*) parameter values of antibiotics in this patient in different periods

date	Cr (c/ μ mol·L^{-1})	CLcr(*f*) (v/mL·min^{-1})	Piperacillin tazobactam		Linezolid		Cefazolin	
			RF	$t_{1/2}$(*f*)(h)	RF	$t_{1/2}$(*f*)(h)	RF	$t_{1/2}$(*f*)(h)
7.15	528.4	12.77	0.41	2.07	0.69	7.49	0.30	7.33
7.19	525	12.85	0.41	2.07	0.69	7.49	0.30	7.31
7.22	488.9	13.80	0.41	2.04	0.70	7.45	0.31	7.12
7.25	361.1	18.69	0.44	1.90	0.71	7.29	0.35	6.38

7.28	222.9	30.27	0.52	1.61	0.75	6.90	0.44	5.02
7.31	183	36.88	0.57	1.48	0.78	6.69	0.49	4.49
8.3	146.3	46.13	0.63	1.34	0.81	6.43	0.56	3.91

Table 3 Comparison of original administration scheme and RF based adjusted administration scheme of antibiotics in different periods

Medication period	Antibiotics	RF (approx.)	Original administration protocol	Adjust the administration plan
07-15—07-25	Piperacillin tazobactam	0.40	4.5 g, q8H	4.5g,q19h 1.8 g, q8H 3.6 g, q16h
07-25—07-31	Piperacillin tazobactam	0.50	4.5 g, q8H	4.5 g,q16h 2.25 g, q8H 0.6 g, q16h
07-25—07-31	Linezolid	0.75	0.6 g,q12h	0.45 g,q12h 0.9 g,q24h 0.6 g,q15h
07-31—08-03	Linezolid	0.80	0.6 g,q12h	0.48 g,q12h 0.96 g,q24h
After 08-03	Cefazolin	0.50	3.0g,q12h	3 g,q24h 1.5 g,q12h

2.2 Comment and Optimization on the rationality of the original administration scheme based on PK / PD

According to the expressions of *f*% *t* > MIC and auic, PK parameters such as VD, F and $t_{1/2}$ of antibiotics and the target flora and MIC should be known for the calculation of them.

Table 1.2 the parameters related to the PK and the antibacterial drugs available in adults (Table 1.2).

2.2.2 The target flora and MIC skin normal flora targeted by antibiotics are mainly Staphylococcus [such as coagulase negative staphylococci (CoNS), Staphylococcus aureus and Streptococcus, and the normal intestinal flora is mainly Enterobacteriaceae. When human immunity is low, these bacteria can become conditional pathogens and cause infection. Epidemiologic analysis shows that immunocompromised patients with diabetes and skin and mucous integrity are vulnerable to staphylococcal skin and soft tissue infections, bloodstream infections and bone and joint infections. In this study, the liver, spleen and pancreas were all damaged. The history of diabetes mellitus, renal insufficiency, immunodeficiency, and multiple skin and soft tissue injuries were accompanied by bleeding. The most probable pathogen was staphylococci, but it could also be Enterobacteriaceae. Based on this and the doctors' judgment experience of infection, Staphylococcus (represented by cons and S. aureus), Enterobacteriaceae and Pseudomonas aeruginosa were selected as the target bacteria for anti

infection. The PK / PD target index based on the rationality evaluation and optimization of the empirical scheme before the microbial culture and drug sensitivity results, and its MIC value is calculated by the sensitivity break point; Based on the PK / MIC value of the optimized microbial culture scheme and the rationality of the subsequent measured PK / MIC value. MIC sensitivity break points and measured values are determined according to the standards formulated by the American Institute of clinical and laboratory standards (CLSI) in 2017 [9], and those not formulated are determined according to the standards formulated by the European Commission for antimicrobial susceptibility testing (eucast) [10], as shown in Table 4.

2.2.3 The target flora of antibiotics in different periods is 07-15-07-25. Piperacillin tazobactam is an empirical drug. The target flora should cover CoNS, *S.aureus*, *Enterobacteriaceae* and *P.aeruginosa*. 07-25 microbial culture results showed that after MRSA, the medication of piperacillin tazobactam on 07-25-07-31 may prevent *Enterobacteriaceae* and *P. aeruginosa infection*, while the medication of linezolid on 07-25-08-03 is aimed at MRSA infection. After linezolid anti MRSA, cefazolin is most likely to experience the prevention of sensitive Staphylococcus (represented by cons and S. aureus) infection after 08-03.

Table 4 break points of MIC sensitivity of antibiotics to target flora（ ρ/ mg ·L-1)

medicine	S. aureus	CoNS	E.beriaceae	P. aeruginosa
Piperacillin tazobactam	≤2	—	≤16⁄4	≤16⁄4
Linezolid	≤4	≤2	—	—
Cefazolin	≤2	—	≤16	—

Note: "-" indicates that neither CLSI nor eucast has been formulated.

2.2.4 PK / PD target index results according to item 2.2.3 and the adjusted administration scheme of each antibacterial drug and the original administration scheme, the *f*% *t* > MIC or AUIC values for different target flora in different periods (see Table 5).

From July 15 to July 25, piperacillin tazobactam had only 1.8 g, q8H and 4.5 g, q8H in each scheme, and the *f*% *t* > MIC of each target flora reached 50%. From July 25 to July 31, piperacillin tazobactam had only 2.25 g, q8H and 4.5 g, q8H in each scheme, and the *f*% *t* > MIC of each target flora reached 50%. From 07-25 to 08-03, the *f*% *t* > MIC of each scheme of linezolid for MRSA was greater than 85%, and the AUIC was 80 ~ 120. From 08 to 03, the *f*% *t* > MIC of cefazolin for the target flora was greater than 50%. Therefore, it can be inferred that these schemes can achieve ideal effects on the target flora in a specific medication period.

Table 5 Comparison of *f*% *t* > MIC or AUIC values of target bacteria in the adjustment scheme and the original scheme of various antibiotics

Medication	Antibiotics	Mic value	12 (t/h)	Administration	S. aureus	CoNS	E.bacteriaceae	P. aeruginosa

period				plan				
07-15—07-25	Piperacillin tazobactam	Sensitive break point meter	2.0	4.5g，q19h	68.5	—	36.9	36.9
				1.8 g， q8H	100	—	54.6	54.6
				3.6 g，q16h	77.3		39.8	39.8
07-25—07-31	Piperacillin tazobactam	Sensitive break point meter	1.66	4.5 g， q8H*	100	—	87.7	87.7
				4.5 g，q16h	—	—	36.4	36.4
				2.25 g， q8H			52.0	52.0
				4.5 g， q8H*	—	—	72.8	72.8
07-25—08-03	Linezolid	Measured value meter	7.0	0.6 g，q16h	100(114.6)	—	—	—
				0.45 g，q12h	100(117.2)	—	—	—
				0.9 g，q24h	100(117.2)			
				0.6g，q12h*	100(152.9)	—	—	—
After 08-03	Cefazolin	Sensitive break point meter	4.0	3 g，q24h	64.3	—	—	—
				1.5 g，q12h	95.2	—	—	—
				3 g，q12h*	100	—	—	—

Note: (1) "-" indicates that the sensitivity break point formulated according to the purpose of medication or due to the lack of CLSI and eucast has not been calculated; (2) * indicates the original clinical administration protocol; (3) Because some literatures classify linezolid as a concentration dependent drug, the data in brackets are the AUIC 0-24 H value. When calculating this value, the value cannot be compared due to different dosing intervals of each scheme. Therefore, the AUIC value per unit time in one dosing interval is used × Adjust for 24 h to obtain comparable AUIC0-24 H values

2.2.5 the rationality evaluation and optimization results of the original administration scheme can be seen from table 5. From 07-15 to 07-25, the *f*% *t* > MIC of piperacillin tazobactam original administration scheme (4.5 g, q8H) and adjusted administration scheme (1.8 g, q8H) for each target flora reached 50%. Theoretically, both schemes have reasonable antibacterial effects. However, compared with the adjusted administration scheme, the high-dose administration of the original administration scheme is bound to cause drug accumulation in patients and increase the risk of adverse reactions.

Therefore, the administration scheme at this stage can be optimized to 1.8 g, q8H. Similarly, from 07-25 to 07-31, the administration scheme of piperacillin tazobactam can be optimized to 2.25 g, q8H; 07-25-8.3, the administration scheme of linezolid can be optimized as 0.6 g, q16h, 0.45 g, q12h or 0.9 g, q24h; 08-03, cefazolin administration scheme can be optimized to 1.5 g, q12h.

2.3 Suggestions on administration scheme

According to the above research, the antibacterial drug administration scheme of the patient should be adjusted and optimized according to its renal function, that is, from 07-15 to 07-25, the administration scheme of piperacillin tazobactam can be 1.8 g, q8H; 07-25-07-31, changed to 2.25

g, q8H; From 07-25 to 08-03, linezolid administration regimen can be 0.6 g, q16h; The renal function of cefazolin can be checked after the administration of q3-08 for 12h, and the renal function can be checked after the administration of q3-08 for 12h.

2.4 Clinical effectiveness verification

Another similar case, a 37 year old male with a body mass of 80 kg, was admitted to hospital on August 7 due to multiple injuries and traumatic shock caused by a car accident. At the time of admission, the patient had swelling and pain in many parts of the body, limited activity, and skin scraping, flushing, ulceration, exudation, edema and so on. The patient was in good health and had no history of other basic diseases and infections. ICU was admitted with "multiple trauma, traumatic shock, rib fracture with pneumothorax, interrupted closed fracture of right tibia and fibula and skin and soft tissue contusion". On the day of admission, it is considered that the patient has fracture, multiple skin scraping, ulceration and exudation, and is vulnerable to S. aureus infection. In clinical experience, tezhixing 4.5g, q8H is used to prevent infection, but the patient's body temperature and Hemogram rise instead of falling after 4 days, and the skin ulceration is red and swollen with yellow pus. Considering the unsatisfactory effect of the drug, it was suspected that it was MRSA infection, so it was replaced with SVO 0.6 g, q12h, and the anti infection treatment was continued. The pharmacist found that the CR of the patient on August 7, 9 and 11 were 153.3 mol / L, 227.5 mol / L and 438.8 mol / L respectively. The decline of renal function showed progressive aggravation, and the administration scheme should be adjusted. Based on the renal function reflected by clcr, the pharmacist optimized the SVO regimen as 0.6 g, q16h (f% t > MIC 100%, AUIC 114.6) or 0.44 g, q12h (f% t > MIC 100%, AUIC 112.1). After explaining the reasons, the pharmacist suggested the doctor to change to the above regimen, and the doctor adopted the 0.6 g, q16h regimen. After 3 days, the patient's body temperature and blood routine returned to normal, and the redness, swelling and pus of the broken skin subsided. It is suggested that the optimized scheme is effective and reflects the renal function reflected by clcr. The optimized scheme is effective, safe and feasible.

3 Discussion

Excessive dosage of penicillins or too fast intravenous drip can lead to a large number of drugs rapidly entering the brain tissue, resulting in the increase of drug concentration in blood and cerebrospinal fluid, resulting in penicillin encephalopathy [13]. Piperacillin has a low serum protein binding rate (30%) and is mainly excreted through the kidney (68%). Even the conventional dose (2 ~ 4 g, q12h) is easy to cause penicillin encephalopathy in patients with renal insufficiency [11]. The CLcr of the patient from 07-15 to 07-31 was 12.6 ~ 36.3 ml / min, the renal function was in the stage of failure, and the liver function was damaged at this time. At this stage, even the conventional dose of piperacillin tazobactam (4 g, q8H based on piperacillin) is bound to increase the blood concentration of free

piperacillin and increase the risk of penicillin encephalopathy. At this stage, the regimen lasted for 16 days. For the process of renal function from failure stage to decompensation stage to compensation stage, the risk of cumulative adverse drug reactions was greatly increased. In addition, the *f*% *t* > MIC of the program for each target flora exceeds 50%. Although the program may have ultra long-term antibacterial effect, the drug clearance is delayed due to the patient's renal insufficiency. The program (relatively large dose or short administration interval compared with the optimized program) not only can not promote the curative effect, but also increases the occurrence of systemic adverse reactions and bacterial drug resistance [12]. The CLcr of the patient was 12.6 ml / min. according to the drug Manual of piperacillin tazobactam (4.5 g recommended when CLcr < 20 ml / min, q12h), the protocol was also inappropriate. Therefore, piperacillin tazobactam administration scheme 07-15-07-25 can be optimized to 1.8 g, q8H; 07-25-07-31, adjusted to 2.25 g, q8H. Theoretically, it is not only effective but also safer.

Although linezolid is not metabolized by liver drug enzymes, only some drugs (about 35%) are excreted through the kidney in the prototype. The drug manual and the clinical medication guide for Chinese doctors and pharmacists also recommend that there is no need to adjust the dose for patients with mild and moderate liver and renal insufficiency. Adult patients with MRSA infection can still be used routinely (0.6 g, q12h). However, according to the Research Report [13-14], the risk of thrombocytopenia and anemia in patients with renal insufficiency is significantly higher than that in patients with normal renal function, which is related to the continuous high concentration of linezolid. At the same time, some scholars also reported that the risk of thrombocytopenia can be effectively reduced or avoided by timely adjusting the dose of linezolid through the monitoring of therapeutic drugs. The patient 07-25-8.3 clcr18 4 ~ 45.4 ml / min, linezolid is used in conventional regimen (0.6 g, q12h) for 9 days. Continuous high concentration of linezolid is bound to lead to potential adverse drug reactions and increase the risk of thrombocytopenia and anemia. When the drug PK / PD target index can reach the target threshold of predicting curative effect, the administration scheme should be adjusted according to the patient's renal function to avoid its adverse reactions. Therefore, 07-25-08-03 linezolid 0.6 g, q16h; The optimization scheme of 0.45 g, q12h or 0.9 g, q24h is not only effective but also safer in theory.

It is worth noting that the main purpose of this study is to explore and optimize the rationality of the original administration scheme based on the renal function reflected by clcr. Therefore, this paper does not explain whether the variety and combination of antibiotics used by patients, the course of treatment and step-down treatment are reasonable. Although the optimization schemes proposed in this paper combine the pharmacodynamic indexes and the renal function of patients, these schemes are only obtained on the premise that other PK parameters, extrarenal clearance and effective plasma concentration of drugs remain unchanged according to the renal clearance of drugs. In fact, there are

differences in efficacy and adverse reactions between different individuals and at different physiological and pathological stages of the same individual. Even for the same individual, in different stages of renal function, the administration scheme should be adjusted according to its condition, especially the drugs cleared through the kidney, so that the administration scheme is effective and can reduce or avoid the occurrence of cumulative adverse reactions. The traffic accident trauma cases in this study show that adjusting the antimicrobial administration scheme based on the renal function reflected by CLcr can formulate a safe, effective, reasonable and feasible administration scheme for patients with renal insufficiency complicated with infection, but only a case shows that the optimization scheme proposed by this method is feasible, and the clinical effectiveness of the optimized scheme needs to be confirmed by more clinical cases.

It should also be noted that for many antibiotics that are metabolized by the liver and not completely excreted from the kidney in clinic, when the liver and kidney function are damaged, it is not completely accurate to adjust the administration scheme only by calculating the renal function. In practice, the author also considers the drug metabolism and excretion pathway and adjusts the administration scheme more accurately in combination with the patient's liver and kidney function. For the investigated drugs in this paper, the limitation of this paper is to adjust the administration scheme by calculating renal function. Nevertheless, for the medication of such patients, when there is no better method to accurately formulate the individualized antibacterial drug administration scheme, the original administration scheme can still be optimized based on the renal function reflected by CLcr in clinical practice as a theoretical guidance to ensure the safe medication.

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