Infection and Drug Resistance

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ORIGINAL RESEARCH

Distribution and Drug Resistance of Pathogenic Bacteria and Prognosis in Patients with Septicemia Bloodstream Infection with Renal Insufficiency

Deng Pan[1,*], Pin Peng[2,*], Yu Fang[3], Jun Lu[3], Minghao Fang[3]

[1]Department of Infectious Disease, Xianning Central Hospital, The First Affiliated Hospital of Hubei University of Science and Technology, Xianning, Hubei, People's Republic of China; [2]Intensive Care Unit, Wuhan Asia General Hospital, Wuhan, Hubei, People's Republic of China; [3]Intensive Care Unit, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China

*These authors contributed equally to this work

Correspondence: Minghao Fang, Intensive Care Unit, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1095 Jiefang Avenue, Wuhan, Hubei, 430030, People's Republic of China, Tel +86-15071157405, Email fangmh@tjh.tjmu.edu.cn

Objective: The aim of this study was to investigate the distribution and drug resistance of pathogenic bacteria and the prognosis of patients with sepsis bloodstream infection with renal insufficiency.

Methods: One hundred and twelve patients with septicemic bloodstream infection with renal insufficiency and 112 patients with septic bloodstream infection without renal insufficiency were selected as study group and control group, respectively. We compare the distribution of pathogenic bacteria, analyze the drug resistance of major bacteria, and compare the efficacy, the incidence of septic shock, duration of mechanical ventilation, hospitalization time, and duration of antimicrobial drug administration between the two groups.

Results: A total of 140 pathogenic strains were isolated from blood cultures in the study group, and 136 strains were isolated from blood cultures in the control group. The sepsis bloodstream infection was mainly caused by Gram-negative bacteria, accounting for 59.42% (164/276). Among the gram-negative bacteria, *Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa*, and *Acinetobacter baumannii* had higher resistance rates to levofloxacin, ceftazidime, piperacillin sodium tazobactam, and amikacin. Among the gram-positive bacteria, *Streptococcus pneumoniae, Enterococcus*, and *Staphylococcus aureus* had high resistance rates to clindamycin, cefazolin, penicillin G, gentamicin, azithromycin, and levofloxacin. The rate of extended spectrum β-lactamase (ESBLs)-producing enterobacteria and multi-drug resistant *Pseudomonas aeruginosa* (MDR-PA) infection was significantly higher in the study group than in the control group; there was no difference in multi-drug resistant *Acinetobacter baumannii* (MDR-AB), vancomycin-resistant *enterococci* (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA) between the two groups. The duration of hospitalization and the duration of antimicrobial drug administration were longer in the study group than in the control group.

Conclusion: The pathogenic bacteria in patients with sepsis bloodstream infection with renal insufficiency are mainly Gram-negative bacteria, are more difficult to be cured, have a longer course of treatment, and need to use antibacterial drugs for a long time.

Keywords: sepsis bloodstream infection with renal insufficiency, pathogenic bacteria, drug resistance, prognosis

Introduction

Sepsis is a serious disease with a mortality rate of up to 25% due to multi-organ dysfunction caused by dysregulation of the body's response to infection and has become a serious health problem worldwide.[1] The number of deaths due to sepsis in the United States accounts for 1/3 of the total number of deaths, and the number of deaths due to sepsis in China likewise amounts to more than 1/3 of the total number of deaths in hospitals. Sepsis in the intensive care unit (ICU) accounts for an even higher mortality rate.[2] Bloodstream infection sepsis is a systemic inflammatory reactive disease of the organism caused by pathogenic bacteria undergoing blood circulation and multiplying, releasing toxins and various metabolites.[3] Older men with multiple comorbidities are more likely to develop bloodstream infection sepsis.[4] It is a serious and highly hazardous infectious disease that predisposes patients to organ failure and death. Renal insufficiency is a chronic progressive damage to the kidneys, resulting in renal atrophy,

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leading to metabolite retention, disruption of acid-base balance and hydromediator balance, and is one of the causative factors of infectious diseases.[5] Patients with renal dysfunction are at increased risk for developing and dying of sepsis.[6] Early anti-infection should be given to patients with sepsis bloodstream infection with renal insufficiency, which can effectively improve the prognosis level of patients and can reduce the morbidity and mortality rate. The diagnostic criterion for bloodstream infection is a positive blood culture, but due to the long period of blood culture testing and the extremely low positive rate, early anti-infection treatment is still based on empirical medication. Knowledge of the distribution characteristics of pathogenic bacteria and bacterial drug resistance in patients with septicemia bloodstream infection with renal insufficiency can provide a basis for clinical decision-making according to their characteristics and their drug resistance. Therefore, this study will investigate the distribution of pathogenic bacteria in patients with sepsis bloodstream infection with renal insufficiency and the impact of prognosis.

Data and Methods

Clinical Data

One hundred and twelve patients with sepsis bloodstream infection with renal insufficiency admitted to our hospital from January 2020 to February 2021 were used as the study group, and 112 patients with sepsis bloodstream infection without renal insufficiency admitted to our hospital during the same period were selected as the control group. This study program is in accordance with the relevant requirements of the Declaration of Helsinki of the World Medical Association.[7]

Inclusion Criteria

(1) meeting the diagnostic criteria of the third international consensus definition of sepsis (Sepsis-3):[8] life-threatening organ dysfunction with a dysregulated host response to infection and a SOFA score ≥2; (2) meeting the diagnostic criteria of the US CDC 1996 for bloodstream infection; (3) renal insufficiency using the diagnostic criteria of Nephrology: blood creatinine 178–707 μmol/L and glomerular filtration rate 10–50 mL/min; all patients and family members gave informed consent and those who signed the informed consent form.

Exclusion Criteria

Exclusion criteria include patients with acute and chronic infectious diseases; those with combined malignant neoplasm, immune system or severe psychiatric diseases; and those with combined infections at other sites.

Methods

Pathogenic Culture and Multi-Drug Resistant Bacteria Detection

In strict accordance with the aseptic practice, 5–10 mL of venous blood was drawn from patients in the early morning on an empty stomach and placed in EDTA anticoagulation tubes, and the serum was separated by centrifugation at 3000 r/min for 5 min under room temperature for 30 min. The strains were identified by VITEK-II microbial automatic identification instrument. A drop of the bacteria was incubated at 37°C with shaking and then placed on standard bacteriology media. Then, all plates were incubated at 37°C for 24–48 h. After incubation, each plate was examined for bacterial identification and antimicrobial susceptibility testing.[9] K-B agar diffusion method was used for the drug sensitivity test of the antibacterial drugs, and the drug sensitivity results were judged according to the American Clinical Laboratory Standardization Institute (CLSI) 2015 standard.[10] Multi-drug resistant bacteria refer to bacteria that present resistance to 3 or more types of antimicrobial drugs at the same time, mainly including multi-drug resistant *Acinetobacter baumannii* (MDR-AB), multi-drug resistant *Pseudomonas aeruginosa* (MDR-PA), extended spectrum β-lactamase (ESBLs) producing *Enterobacteriaceae*, vancomycin-resistant *enterococci* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA). Pathogenic bacteria exclude fixed values with contaminating strains, and the same strains were calculated according to the same strains in the same patient who sent specimens multiple times for detection.

Treatment Method

Patients in both groups were treated with appropriate antibacterial drugs based on pathogenic bacteria and drug sensitivity test results, and patients with severe renal insufficiency were treated with bedside hemodialysis.

Observation Index

We compare the distribution of drug-resistant bacteria in the two groups.

Analyze the drug resistance of major gram-negative bacteria.

we compare the efficacy, incidence of septic shock, duration of mechanical ventilation, hospital stay, and duration of antimicrobial drug administration between the two groups.

The efficacy was determined: Significant effect: after 7 days of treatment, clinical symptoms and signs such as rapid heartbeat and respiratory rate disappeared or improved significantly, body temperature returned to below 38°C, and white blood cell count and blood culture returned to normal; Effective: clinical symptoms and signs such as rapid heartbeat and respiratory rate improved, and white blood cell count and blood culture were basically close to normal; Ineffective: none of the above clinical symptoms and signs improved or worsened. Total effective rate = apparent rate + effective rate.

Statistics

SPSS 23.0 software was applied for statistical analysis of the data. All data were subjected to normality test and chi-square test, and the measurement data were expressed by Mean ± SD. *t*-test was used to measure data between groups, and the difference was considered statistically significant at $P<0.05$.

Results

Comparison of General Information Between the Two Groups

General data such as age, gender, BMI, disease causation, liver function, and antimicrobial drug use were compared between the two groups and no statistical differences were found, as shown in Table 1.

Comparison of the Distribution of Pathogenic Drug Bacteria

A total of 140 pathogenic strains were isolated from blood cultures in the study group, and 136 strains were isolated from blood cultures in the control group. The sepsis bloodstream infection was mainly caused by Gram-negative bacteria, and Gram-negative bacteria accounted for 59.42% (164/276). Gram-negative bacteria in the study group were lower than those in the control group, and Gram-positive bacteria were significantly higher than those in the control group, as shown in Table 2.

Drug Resistance in Common Gram-Negative Bacteria

Among the Gram-negative bacteria isolated from both groups, *Klebsiella pneumoniae* had higher resistance rates to ceftriaxone, levofloxacin, ceftazidime, piperacillin sodium tazobactam, amikacin, minocycline, amoxicillin, and the

Table 1 Comparison of General Information of Each Group

Item	Study group (112)	Control Group (112)	t/χ^2	P
Age (years)	54.92±11.56	54.78±11.46	0.091	0.928
Gender (male/female)	61/51	63/49	0.072	0.788
BMI (kg/m2)	24.78±3.49	24.83±3.53	−0.107	0.915
Disease severity				
Sequential organ failure score (points)	5.63±1.02	5.43±1.09	1.418	0.158
Acute physiological and chronic health score (points)	22.18±2.34	22.09±2.29	0.291	0.771
Disseminated intravascular coagulation score (points)	3.11±0.78	3.06±0.83	0.465	0.642
Infection causation (n)				
Surgical	67(59.82)	69(61.61)	0.075	0.784
Internal medicine	45(40.18)	43(38.39)	0.075	0.784
Diabetes mellitus (n)	37(33.04)	35(31.25)	0.082	0.775
Chronic obstructive pulmonary disease (n)	20(17.86)	22(19.64)	0.117	0.732
Impaired consciousness (n)	52(46.43)	54(48.21)	0.996	0.072
Hepatic insufficiency (n)	16(14.28)	13(11.61)	0.356	0.551
Invasive operations (n)	51(45.54)	48(42.86)	0.163	0.686
Preventive use of antimicrobial drugs (n)	78(69.64)	75(66.96)	0.186	0.666

Table 2 Comparison of the Distribution of Drug-Resistant Bacteria Between the Two Groups n (%)

Pathogenic Bacteria n (%)	Study Group (140)	Control Group (136)	χ^2	P
Gram-negative bacteria	71(50.71%)	93(68.38%)	11.018	0.001
Klebsiella pneumoniae	29(20.71%)	38(27.94%)		
Escherichia coli	8(5.71%)	20(14.71%)		
Acinetobacter baumannii	16(14.29%)	26(19.12%)		
Pseudomonas aeruginosa	6(4.29%)	6(4.41%)		
Other	2(1.43%)	3(2.21%)		
Gram-positive bacteria	57(40.71%)	36(32.14%)	8.108	0.004
Staphylococcus epidermidis	6(4.29%)	4(2.94%)		
Glucococcus aureus	11(7.86%)	9(6.62%)		
Enterococcus	16(11.43%)	10(7.35%)		
Listeria monocytogenes	4(2.86%)	2(1.47%)		
Pneumococcus spp.	6(4.29%)	3(2.21%)		
Streptococcus pneumoniae	10(7.14%)	4(2.94%)		
Other	4(2.86%)	4(2.94%)		
Fungi	12(8.57%)	7(5.15%)	1.438	0.230
Pseudomonas albicans	3(2.14%)	2(1.47%)		
Aspergillus	6(4.29%)	3(2.21%)		
Other	3(2.14%)	2(1.47%)		

lowest resistance rate to tigecycline; *Escherichia coli* had higher resistance rates to levofloxacin, ceftazidime, ceftriaxone, piperacillin sodium tazobactam, amikacin, imipenem, Cefoperazone sodium sulbactam sodium, minocycline, and the lowest resistance rate to amoxicillin and tigecycline; *Pseudomonas aeruginosa* had a higher resistance rate to levofloxacin, cefoperazone sodium sulbactam sodium, ceftazidime, piperacillin sodium tazobactam, amikacin, imipenem; *Acinetobacter baumannii* had a higher resistance rate to ceftazidime, levofloxacin, piperacillin sodium tazobactam, imipenem, cefoperazone sodium sulbactam sodium, amikacin, amoxicillin and tigecycline, as shown in Table 3.

Drug Resistance of Common Gram-Positive Bacteria

Among the Gram-negative bacteria isolated from the two groups of patients, *Streptococcus pneumoniae* had higher resistance rates to clindamycin, cefazolin, penicillin G, gentamicin, azithromycin, levofloxacin, cotrimoxazole, and rifampin; *Enterococci* had higher resistance rates to clindamycin, azithromycin, cefazolin, levofloxacin, gentamicin, penicillin G, and vancomycin; S*taphylococcus aureus* had higher resistance rates to penicillin G, clindamycin, azithromycin, cefazolin, gentamicin, levofloxacin, rifampicin and compound sulfamethoxazole had higher resistance rates, as shown in Table 4.

Table 3 Drug Resistance in Common Gram-Negative Bacteria n (%)

Pathogenic Bacteria	*Klebsiella pneumoniae* (67)	*Escherichia coli* (28)	*Pseudomonas aeruginosa* (12)	*Acinetobacter baumannii* (42)
Tigecycline	5(7.46)	3(10.71)	–	9(21.43)
Amikacin	30(44.78)	13(46.43)	6(50.00)	22(52.38)
Levofloxacin	38(56.72)	16(57.14)	8(66.67)	31(73.81)
Imipenem	25(37.31)	10(35.71)	5(41.67)	27(64.29)
Cefoperazone	29(43.28)	10(35.71)	7(58.33)	24(57.14)
Ceftriaxone	42(62.69)	15(53.57)	–	–
Ceftazidime	38(56.72)	16(57.14)	7(58.33)	34(80.95)
Piperacillin	34(50.75)	15(53.57)	6(50.00)	30(71.43)
Amoxicillin	7(10.45)	3(10.71)	–	13(30.95)
Minocycline	9(13.43)	6(21.43)	–	–

Table 4 Drug Resistance of Common Gram-Positive Bacteria n (%)

Pathogenic Bacteria	*Streptococcus pneumoniae* (14)	*Enterococcus* (26)	*Staphylococcus aureus* (20)
Linezolid	0	0	0
Vancomycin	0	2(7.69%)	0
Gentamicin	9(64.29%)	12(46.15%)	12(60.00%)
Compound sulfamethoxazole	6(42.86%)	–	7(35.00%)
Rifampicin	6(42.86%)	–	8(40.00%)
Levofloxacin	8(57.14%)	14(53.85%)	11(55.00%)
Clindamycin	10(71.43%)	24(92.31%)	15(75.00%)
Azithromycin	9(64.29%)	23(88.46%)	15(75.00%)
Cefazolin	10(71.43%)	17(65.38%)	14(70.00%)
Penicillin G	8(66.67%)	21(18.75%)	17(85.00%)

Comparison of Multi-Drug Resistant Bacterial Infections Between the Two Groups

The two groups of multi-drug resistant bacteria infections were compared, and it was found that the rate of ESBLs-producing Enterobacteriaceae and MDR-PA infections was significantly higher in the study group than in the control group, while the difference was not statistically significant when comparing MDR-AB, VRE and MRSA in the two groups, see Table 5.

Comparison of the Efficacy of the Two Groups

In addition, we compared the total effective rate of treatment between the two groups and found no difference in the total effective rate between the two groups, as shown in Table 6.

Comparison of the Incidence of Septic Shock, Duration of Mechanical Ventilation, Length of Hospitalization, and Duration of Antimicrobial Drug Administration Between the Two Groups

The length of hospital stay and duration of antimicrobial drug administration in the two groups were counted, and it was found that the length of hospital stay and duration of antimicrobial drug administration in the study group were significantly longer than those in the control group; there was no difference in the incidence of septic shock and duration of mechanical ventilation between the two groups, as shown in Table 7.

Table 5 Comparison of Multi-Drug Resistant Bacterial Infections Between the Two Groups

Pathogenic Bacteria n(%)	Study Group (112)	Control Group (112)	χ^2	P
MDR-AB	7(6.25%)	5(4.46%)	0.352	0.553
MDR-PA	9(8.04%)	4(3.57%)	2.042	0.153
ESBLs	38(33.93%)	24(21.43%)	4.371	0.366
VRE	0	2(1.79%)	2.018	0.155
MRSA	10(8.93%)	7(6.25%)	0.573	0.449

Abbreviations: MDR-AB, multi-drug resistant *Acinetobacter baumannii*; MDR-PA, multi-drug resistant *Pseudomonas aeruginosa*; extended spectrum β-lactamase producing *Enterobacteriaceae*; VRE, vancomycin-resistant *enterococci*; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 6 Comparison of the Efficacy of the Two Groups n (%)

Indicator	Study Group (112)	Control Group (112)	χ^2	P
Apparent effect	12(10.71%)	16(14.29%)		
Effective	4(3.57%)	5(1.79%)		
Ineffective	96(85.71%)	91(81.25%)		
Total effective rate n (%)	16(14.29%)	21(18.75%)	0.809	0.368

Table 7 Comparison of the Incidence of Septic Shock, Duration of Mechanical Ventilation, Length of Hospital Stay, and Duration of Antimicrobial Drug Administration Between the Two Groups ($\overline{X}\pm s$)

Indicator	Study Group (112)	Control Group (112)	x^2/t	P
Incidence of septic shock (n)	10(8.93%)	7(6.25%)	0.573	0.449
Duration of mechanical ventilation (d)	11.37±2.39	10.83±2.76	1.565	0.119
Length of hospitalization (d)	21.78±4.01	18.49±3.91	6.217	<0.001
Duration of antimicrobial drug administration (d)	18.93±3.37	15.03±3.02	9.121	<0.001

Discussion

Sepsis is a common complication of severe trauma, burns, shock, infection and major surgical procedures, with typical clinical symptoms, such as drowsiness, impaired consciousness, oliguria and cough, which progresses more rapidly and can develop into a multi-organ dysfunction syndrome and even lead to death without timely and effective treatment.[11] Bloodstream infection is a clinical emergency, and the disease progresses rapidly.[12] Renal insufficiency is a group of diseases caused by the destruction of renal tissues, the decrease in glomerular filtration function, and the decrease in the ability of the kidneys to detoxify from various causes, resulting in impairment of the body's ability to regulate electrolyte balance and excrete metabolites.[13] The sepsis bloodstream infection with renal insufficiency will not only increase the condition, but also increase the difficulty of treatment, which is extremely detrimental to the prognosis of patients.[14] Currently, anti-infective therapy is often used to treat patients with sepsis bloodstream infection with renal insufficiency, and anti-infective therapy requires analysis of the distribution of pathogenic bacteria in patients in order to improve clinical efficacy. Recent studies pointed out that renal insufficiency is one of the main high-risk factors for associated multi-drug resistant bacterial infections, and the distribution of pathogenic bacteria may not be identical between patients with hemorrhagic infection with renal insufficiency and non-renal patients.[15,16] At present, there is a lack of clinical guidelines and expert consensus on the treatment of patients with septicemic bloodstream infection with renal insufficiency, and the relevant literature is scarce, which is therefore not conducive to the empirical use of anti-infective therapy and the selection of antimicrobial drugs in clinical practice.

One study pointed out that the infecting pathogens in patients with bloodstream infection sepsis were predominantly Gram-negative bacteria.[17] Our study showed that sepsis bloodstream infection was mainly caused by Gram-negative bacteria, with Gram-negative bacteria accounting for 59.42% (164/276), which is consistent with the results of the above study, suggesting that Gram-negative bacteria were the predominant infecting pathogens in patients with sepsis bloodstream infection with renal insufficiency. However, some studies have also found that Gram-positive bacteria are the predominant infecting pathogens in patients with septicemia bloodstream infection.[18] This discrepancy may be due to geographical differences, and therefore clinicians should refer to the local distribution of blood culture pathogens during the clinical selection of antimicrobial drugs for empirical use. It is worth noting in the clinic that because Gram-negative bacteria are widely distributed in the body, they can cause infection in the organism under certain conditions, and

bloodstream infections caused by them are more serious and have a higher morbidity and mortality rate than those induced by Gram-positive bacteria.

Gram-negative bacilli have increasing rates of resistance to antimicrobial drug-resistant drugs. When grouped and analyzed in ICU, non-ICU inpatient and emergency departments, the highest detection rates were *Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, respectively.[19] *Klebsiella pneumoniae* has extensive drug resistance, limited choice of therapeutic drugs and easy dissemination, which poses a great challenge to clinical infection treatment.[20] A study by Lee[21] et al pointed out that *Klebsiella pneumoniae* had a high rate of resistance to amikacin and others; *Acinetobacter baumannii* had a high resistance rate of about 70% to imipenem and a relatively low rate of resistance to tigecycline.[22] A study by Huseh[23] et al noted that *Escherichia coli* had high resistance to levofloxacin, ceftriaxone, and ceftazidime. The results of this study suggested that *Klebsiella pneumoniae* had a high resistance rate to ceftriaxone, levofloxacin, ceftazidime, piperacillin, amikacin, minocycline, and amoxicillin, and the lowest resistance rate to tigecycline; *Escherichia coli* resistance rate to levofloxacin, ceftazidime, ceftriaxone, piperacillin, amikacillin, imipenem, cefoperazone, and minocycline, and to amoxicillin and tigecycline lowest. The resistance rate of *Pseudomonas aeruginosa* to levofloxacin, cefoperazone, ceftazidime, piperacillin, amikacin and imipenem was higher; the resistance rate of *Acinetobacter baumannii* to ceftazidime, levofloxacin, piperacillin, imipenem, cefoperazone, amikacin, amoxicillin and tigecycline was higher. In recent years, hospital-acquired infections induced by Gram-positive bacteria have been increasing year by year. The resistance of different Gram-positive bacteria to antibacterial drugs varies.[24] But we can still find some similarities. Biagio Santella et al found that Gram-positive bacteria were highly resistant to penicillin G and oxacillin,[9] and the same high level of resistance to penicillin G was found for Gram-positive bacteria in our study. Therefore, in the clinical treatment of patients with sepsis bloodstream infection with renal insufficiency, sensitive antimicrobial drugs should be selected according to the results of pharmacological examination, and antimicrobial drugs that have developed resistance should be avoided as much as possible, and the drug regimen should be adjusted timely according to the actual situation of patients.

Our study has some limitations. The sample size of this study was small and the age of patients was not differentiated, and the age of patients should be differentiated at a later stage on the basis of expanding the sample size. In addition, all patients in the study were from our hospital, which could not reflect the effect of geographic differences in different pathogenic bacteria on the results, and these need to be further studied in the future.

In conclusion, the pathogenic bacteria in patients with sepsis bloodstream infection with renal insufficiency are predominantly Gram-negative bacteria, and patients with sepsis bloodstream infection with renal insufficiency are more difficult to cure, have a longer course of treatment, and require prolonged use of antimicrobial drugs.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding authors on reasonable requests.

Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. Informed consent was obtained from all the study subjects before enrollment.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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