Community-Acquired *Klebsiella pneumoniae* Complicated Skin and Soft-Tissue Infections of Extremities: Emphasis on Cirrhotic Patients and Gas Formation

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Abstract

Background: *Klebsiella pneumoniae* was rarely reported to cause complicated skin and soft tissue infections (cSSTIs). Our study was to delineate clinical characteristics and outcome of cSSTIs involving extremities caused by *K. pneumoniae*.

Patients and Methods: Adult patients aged 16 years or more with community-acquired cSSTIs, which involved the extremities and were caused by four common aerobic pathogens at a medical center in southern Taiwan during a 54-month period, were reviewed.

Results: Of 76 cases enrolled, *Staphylococcus aureus* was the most common pathogen (52 cases, 68%), followed by *K. pneumoniae* (16, 21%), β-hemolytic streptococci (5, 7%), and *Escherichia coli* (3, 4%). Forty-six (61%) had underlying conditions, and diabetes mellitus was most common among *K. pneumoniae* and non-*K. pneumoniae* groups (63% and 45%, respectively). Compared to patients with cSSTIs caused by other bacteria, those with *K. pneumoniae* cSSTIs were predominantly male, more often had liver cirrhosis, malignant neoplasm and alcoholism. In addition, they were more likely to have fever, shock, bacteremia, gas formation, pyomyositis, metastatic infections, as well as longer durations of hospitalization. Using multivariate analysis, liver cirrhosis (adjusted odds ratio [aOR] 12.5, 95% confidence interval [CI] 2.0–79.1, $p = 0.007$) and male gender (aOR 11.5, 95% CI 1.1–116.8, $p = 0.039$) were significantly associated with *K. pneumoniae* cSSTIs.

Conclusions: We highlight the role of *K. pneumoniae* in Taiwanese patients with cSSTIs involving extremities, and its potential for gas and pus formation, and metastatic infections. Empiric antimicrobial coverage of *K. pneumoniae* and close monitoring of metastatic infections are mandatory for patients with risk factors.

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Introduction

Complicated skin and soft tissue infection (cSSTI) of the extremities is one of the reasons for the frequent visits to health care providers. Most of the cases are caused by *Staphylococcus aureus* and aerobic streptococci [1–3], while facultative gram-negative bacilli, including *Klebsiella pneumoniae*, are uncommon causes of community-acquired cSSTIs of the extremities [1–4]. Irrespective of iliopsoas abscess, by reviewing the literature on MEDLINE from 1970 to 2005, less than 30 cases of cSSTIs of the extremities caused by monomicrobial *K. pneumoniae* were reported [5–17].

In Taiwan, *K. pneumoniae* has been noted as a major pathogen of liver abscess [18–20], endophthalmitis [21, 22], gram-negative bacillary meningitis [23–25], brain abscess [26, 27], lung abscess [28], thoracic empyema [29], prostatic abscess [30], and deep neck infection [31, 32]. Our previous study also found that *K. pneumoniae* is not an uncommon pathogen of psoas muscle abscess [33]. Since we have come across several cases of cSSTIs of the extremities caused by *K. pneumoniae*, and since their

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characteristics have never been reported in the literature, a retrospective study was conducted to delineate the epidemiological features, clinical characteristics, and outcome of cSSTIs of the extremities caused by *K. pneumoniae*, in comparison with those caused by pathogens other than *K. pneumoniae*.

Patients and Methods

Patients

This retrospective study was conducted at National Cheng Kung University Hospital (NCKUH), a 900-bed academic medical center in southern Taiwan. We reviewed the records of the microbiological laboratory from July 1995 to December 1999 for *K. pneumoniae*, *Staphylococcus* species, *Streptococcus* species, and *Escherichia coli*, which accounted for > 90% of aerobic causes of cSSTIs of the extremities [1–3]. Patients aged ≥ 16 years with community-acquired cSSTIs of the extremities were identified by chart reviews. The diagnoses of cSSTIs were based on clinical, roentgenographic, surgical or histopathologic findings. Infections of head and neck, trunk, psoas muscle, perineum, and cutaneous inflammation overlying septic arthritis were excluded because of the complex anatomic structures and different predisposing factors. Polymicrobial infections were also excluded. Community-acquired infection was defined as that, which occurred before or within 48 h of hospital admission. For patients with recurrent cSSTIs, only the first episode was enrolled.

Data Collection

Clinical information of initial presentations, demographic data, underlying diseases, laboratory findings on admission, and treatment courses were retrieved. Follow-up information on August 2004 was obtained from medical records for repetitive infections and clinical outcomes. Pathogens must be isolated from tissue/fluid specimens obtained by surgical debridement or needle aspiration. The identification of microorganisms was based on colonial morphology and biochemistry reactions. Antimicrobial susceptibility was determined by disk diffusion method, as described by the Clinical and Laboratory Standards Institute [34].

Fever was defined as a tympanic temperature of 37.8 °C or more. Shock was defined as a decrease in systolic blood pressure to less than 90 mmHg or a decrease of more than 30 mmHg from baseline. Diabetes mellitus was diagnosed according to the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus Criteria [35]. The diagnosis of liver cirrhosis was based on sonographical, laboratory and clinical findings. Metastatic infections were considered present, if the same microorganism was isolated from other normally sterile body sites. A fatal case was defined as the death of a patient within 14 days of admission. A repetitive infection was defined as an infection by the same organism in any normally sterile body site before or after the study episode with a 2-month disease-free interval. If the infection recurred in the same site within 2 months, the case was regarded as having a relapsing infection.

Statistical Analysis

To identify risk factors associated with *K. pneumoniae* infections, we compared patients with cSSTIs of the extremities caused by *K. pneumoniae* to those caused by other aerobic pathogens, including *Staphylococcus* species, *Streptococcus* species, and *E. coli.* Continuous data were expressed as mean value ± standard deviation (SD), and were compared by Student's *t*-test or Mann-Whitney *U*-test. Categorical variables, expressed as numbers and percentages, were compared by χ^2 test or Fisher's exact test. The level of significance was set at 0.05. For multivariate analysis, variables that were significant in the univariate analysis, potential confounders, and those regarded as risk factors in previous studies of *K. pneumoniae* infections were included. We first evaluated the collinearity among variables and selected variables representing independent risks of disease severity. Stepwise backward elimination of nonsignificant variables was then conducted to arrive at the final model.

Results

During the 54-month period, 76 patients with pathogen-verified cSSTIs of the extremities were enrolled in this study. Among them, oxacillin-susceptible *S. aureus* was the most common pathogen (52 cases, 68.4%), followed by *K. pneumoniae* (16, 21.1%), β-hemolytic streptococci (5, 6.6%), and *E. coli* (3, 3.9%). The patient population comprised 50 men and 26 women, and their age ranged between 17 and 85 years, with a mean age of 53.4 years. The median interval between onset of symptoms and diagnosis was 5 days, with a range from 1 to 30 days. Fifty-four (71%) patients involved lower extremities. The diagnoses of cSSTIs included subcutaneous abscess in 23 (30.3%) cases, cellulites in 20 (20.6%), pyomyositis in 17 (22.4%), and necrotizing fasciitis in 16 (21.1%).

The clinical characteristics of patients with cSSTIs of the extremities caused by *K. pneumoniae* and pathogens other than *K. pneumoniae* were compared in Table 1. Patients with cSSTIs caused by *K. pneumoniae* were predominantly males (94% vs 58%, $p = 0.008$), had a higher prevalence of liver cirrhosis (38% vs 7%, $p = 0.005$), malignant neoplasm (31% vs 3%, $p = 0.004$), and alcoholism (31% vs 8%, $p = 0.03$). The other factors, such as age, nativity, trauma, diabetes mellitus, and other underlying diseases were not significantly different between the two groups.

To evaluate the host factors in association with *K. pneumoniae* in patients with cSSTIs of the extremities, the results of a multivariate analysis were shown in Table 2. While assessing the variables, liver cirrhosis and malignant neoplasm were found to have a correlation (Pearson correlation = 0.375, $p = 0.001$), partially because three patients have liver cirrhosis and hepatocellular carcinoma. Therefore, only liver cirrhosis was selected to be included into the multivariate analysis. After adjustment of the variables significant in the univariate analysis, liver cirrhosis (adjusted odds ratio [aOR] 12.5, 95% confidence interval [CI] 2.0–79.1, $p = 0.007$) and male gender (aOR 11.5, 95% CI 1.1–116.8, $p = 0.039$) were associated with presence of *K. pneumoniae* cSSTIs. As for initial laboratory findings, there was no significant difference among patients with cSSTIs caused by *K. pneumoniae* and those by pathogens other than *K. pneumoniae* (Table 3).

The intervals between symptom onset and clinical diagnosis were on average 7 days in patients with *K.*

Table 1
Comparison of clinical characteristics between patients with *Klebsiella pneumoniae* and non-*K. pneumoniae* complicated skin and soft tissue infections of extremities.

Variables[a]	*K. pneumoniae* (n = 16)	Non-*K. pneumoniae* (n = 60)	*p*-Value
Age (years)	51.5 ± 14.0	53.8 ± 17.9	0.637
Male	15 (93.8)	35 (58.3)	0.008[b]
Nativity of Taiwan	15 (93.8)	59 (98.3)	0.379[b]
Underlying diseases[c]			
Diabetes mellitus	10 (62.5)	27 (45.0)	0.213
Liver cirrhosis	6 (37.5)	4 (6.7)	0.005[b]
Malignant neoplasm	5 (31.3)	2 (3.3)	0.004[b]
Nephrotic syndrome	1 (6.3)	1 (1.7)	0.379[b]
Glucorticosteroid therapy[d]	1 (6.3)	1 (1.7)	0.379[b]
Myelodysplastic syndrome	0	1 (1.7)	> 0.99[b]
HIV infection	0	1 (1.7)	> 0.99[b]
Alcoholism	5 (31.3)	5 (8.3)	0.03
Trauma	6 (37.5)	28 (46.7)	0.512

[a]Data are presented with mean ± standard deviation or number of patients (%); [b]by Fisher's exact test; [c]some patients had more than one underlying diseases; [d]at least 10 mg prednisolone every day

pneumoniae cSSTIs, and about 10 days in those with non-*K. pneumoniae* cSSTIs. At initial presentation, more patients with *K. pneumoniae* cSSTIs had fever (88% vs 52%, $p = 0.01$), shock (31% vs 7%, $p = 0.017$), focal gas formation (38% vs 0%, $p < 0.001$), and concurrent bacteremia (43% vs 17%, $p = 0.038$) and development of metastatic infections (25% vs 3%, $p = 0.016$). The proportions of patients with focal bullae formation, undergoing surgical debridement, and repetitive infections after discharge were similar. In addition, patients with *K. pneumoniae* cSSTIs had longer durations of hospitalization than those with cSSTIs caused by other pathogens (45 ± 50 vs 17 ± 13 days, $p = 0.039$) (Table 4).

Of these 76 patients with cSSTIs of the extremities, all six with gas formation noted on plain X-ray films or computed tomography scans were infected by *K. pneumoniae* (Figure 1). All had underlying diseases, including diabetes mellitus (four cases), alcoholic liver cirrhosis (three, and one concurrent diabetes mellitus), and rectal cancer (one with diabetes). Three of them had concurrent bacteremia and shock.

Table 2
Multivariate analysis of host factors associated with *K. pneumoniae* infections in patients with complicated skin and soft tissue infections involving the extremities.

Variables	Adjusted odds ratio	95% Confidence interval	*P*-Value
Liver cirrhosis	12.5	2.0–79.1	0.007
Male gender	11.5	1.1–116.8	0.039
Diabetes mellitus	2.2	0.6–9.0	0.255
Alcoholism	2.3	0.4–12.1	0.320

The development of *K. pneumoniae* metastatic infections, which were microbiologically verified, were found in four patients, including liver abscess in a diabetic patient, endophthalmitis in a patient with diabetes and rectal cancer, urinary tract infection in a patient with liver cirrhosis and hepatocellular carcinoma, and soft tissue infection in the opposite limb in a patient with alcoholic liver cirrhosis. Three of them had concurrent bacteremia. Based on the radiological imaging, contiguous osteomyelitis was found in three (18.8%) patients. In the non-*K. pneumoniae* group, a patient developed infection in the left foot and buttock, and another patient in the right hand and buttock. Both were diabetic and the infections were caused by *S. aureus*.

All 16 patients with *K. pneumoniae* cSSTIs of the extremities were hospitalized and were treated with intravenous antibiotics. Fifteen patients underwent surgical debridement and one received needle aspiration of focal abscess. Of note, cSSTIs by *K. pneumoniae* were more likely to cause pyomyositis than those by other pathogens (56.3% vs 13.3%, $p < 0.001$). No patient with *K. pneumoniae* cSSTIs died during hospitalization.

In an average follow-up period of 43 months, two patients had repetitive *K. pneumoniae* infections. One had recurrent infection in the above-knee amputation stump 8 months later. The other patient developed liver abscess 1 year later. Moreover, a patient had orchitis due to *K. pneumoniae* and *Enterococcus* 4 years prior to the index episode. All the above three patients had diabetes melli-

Table 3
Comparison of initial laboratory data between patients with complicated skin and soft tissue infections of the extremities caused by *K. pneumoniae* and those by pathogens other than *K. pneumoniae*.

Variables[a]	*K. pneumoniae* (n = 16)	Non-*K. pneumoniae* (n = 60)	*P*-Value
Leukocyte ($\times 10^3/mm^3$)	12.1 ± 6.3	15.0 ± 8.7	0.217
Total lymphocyte (per mm^3)	917.8 ± 535.3	1,369.8 ± 1,120.1	0.123
Hemoglobin (g/dl)	11.8 ± 2.2	13.0 ± 2.3	0.074
Platelet ($\times 10^3/mm^3$)	203.2 ± 193.0	240.8 ± 114.2	0.423
C-reactive protein (mg/dl)	175.8 ± 122.2	143.9 ± 143.2	0.440
Blood urea nitrogen (mg/dl)	23.1 ± 13.0	22.1 ± 19.6	0.845
Serum creatinine (mg/l)	1.3 ± 0.7	1.3 ± 1.0	0.862
Serum AST (IU/l)	62.6 ± 54.3	50.5 ± 49.6	0.400
Serum ALT (IU/l)	63.7 ± 39.0	62.9 ± 106.0	0.979
Serum fasting glucose (mg/dl)	287.6 ± 192.9	206.7 ± 166.6	0.103

AST: aspartate aminotransferase, ALT: alanine aminotransferase; [a]All data are presented as mean value ± standard deviation

Table 4
Clinical manifestations and outcome of 76 patients with complicated skin and soft tissue infections of extremities caused by *K. pneumoniae* and those by pathogens other than *K. pneumoniae*.

Variables[a]	*K. pneumoniae* (n = 16)	Non-*K. pneumoniae* (n = 60)	*P*-Value
Duration between onset and diagnosis (days)	7.6 ± 7.2	9.8 ± 13.7	0.540
Duration of hospital stay (days)	45.4 ± 50.4	16.7 ± 12.8	0.039
Right side infection	10 (62.5)	27 (45.0)	0.213
Fever (>37.8 °C)	14 (87.5)	31 (51.7)	0.010[b]
Shock	5 (31.3)	4 (6.7)	0.017[b]
Bullae formation	3 (18.8)	9 (15.0)	0.708[b]
Focal gas formation	6 (37.5)	0	< 0.001[b]
Bacteremia	6/14 (42.9)	9/53 (17.0)	0.038
Metastatic infections	4 (25.0)	2 (3.3)	0.016[b]
Category of soft tissue infections			0.001
Cellulitis	1 (6.3)	19 (31.7)	
Subcutaneous abscess	2 (12.5)	21 (35.0)	
Pyomyositis	9 (56.3)	8 (13.3)	
Necrotizing fasciitis	4 (25.0)	12 (20.0)	
Receipt of surgical debridement	15 (93.8)	41 (68.3)	0.055[b]
Repetitive infections	2 (12.5)	5 (8.3)	0.634[b]
Fatality	0	3 (5.0)	> 0.99[b]

[a]Data are presented with mean ± standard deviation or number of patients (%); [b]by Fisher's exact test

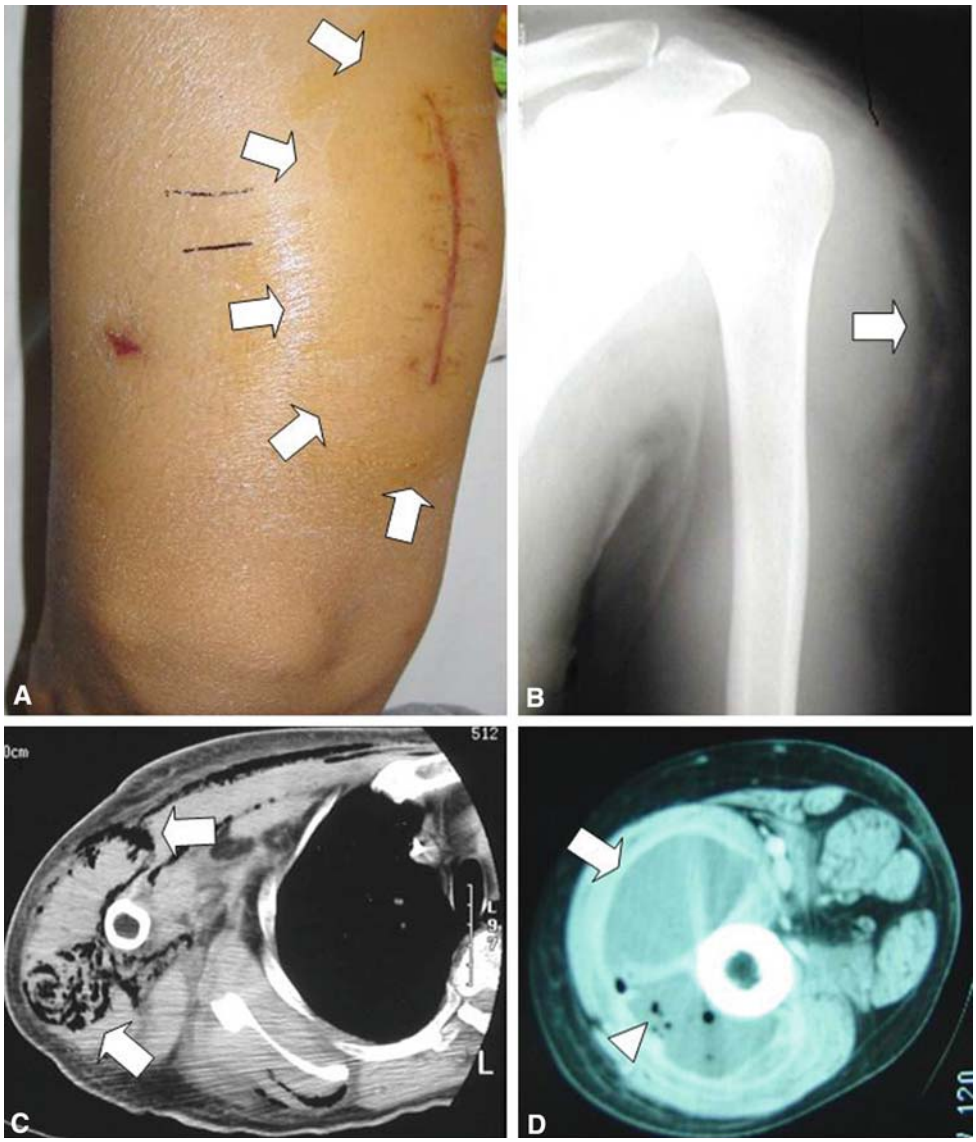

Figure 1. Clinical pictures of complicated skin and soft tissue infections of extremities caused by *K. pneumoniae*. A. Swelling of right thigh (indicated by arrows) in a patient with subcutaneous abscess. B. Gas in left deltoid muscle (arrow) on X-film. C. Gas in right deltoid muscle and anterior chest wall (arrows) in computed tomography. D. Loculated abscesses with gas (arrowhead) and rim enhancement (arrow) on contrasted computed tomography.

tus. In the non-*K. pneumoniae* group, the repetitive infections in five patients were caused by *S. aureus*, and four of them were diabetic. Except for one isolate resistant to second generation cephalosporins and netilmycin and two to chloramphenicol, all *K. pneumoniae* isolates were resistant to ampicillin but susceptible to fluoroquinolones.

Discussion

In Taiwan, *K. pneumoniae* is well known as a common cause of pyogenic infections. Our findings further highlight the role of *K. pneumoniae* as an important pathogen of cSSTIs of the extremities. Patients with *K. pneumoniae* cSSTIs were predominantly male, more often had liver cirrhosis, malignant neoplasm and alcoholism, and are more likely to have fever, shock, concurrent bacteremia, and focal gas formation at initial presentation, suggestive of more severe and complicated infectious processes. Besides, they needed longer durations of hospitalization, and were more likely to develop metastatic infections. To our knowledge, this is the first study focusing on *K. pneumoniae* cSSTIs in the extremities.

It is unusual to note the association of liver cirrhosis and *K. pneumoniae* cSSTIs. Though the high susceptibility of cirrhotic patients to infection has been ascribable to the impairment of hepatic reticuloendothelial function [36] and cell-mediated and humoral immunity [37, 38], the reason for their clinical interaction remains obscure. However, the following scenario could be feasible. Upon translocation from the gut, escape of enteric *K. pneumoniae* from phagocytosis by the impaired hepatic reticuloendothelial system, will result in the development of transient bacteremia, followed by bacterial seeding at the extremities.

Diabetes mellitus has been closely associated with *K. pneumoniae* infections in many studies [19,26–31,33,39]. Although *K. pneumonia* is a common pathogen of cSSTIs in diabetic patients, such an association between diabetes and *K. pneumoniae* SSTIs is not apparent in the present study. It is probable that diabetes mellitus is a common predisposing factor of cSSTIs of the extremities, irrespective of the causative pathogens.

Metastatic infection is an important complication in *K. pneumoniae* liver abscess [20, 21, 40], and not surprisingly, it was found in patients with *K. pneumoniae* cSSTIs of the extremities. Since all four patients with *K. pneumoniae* cSSTIs and metastatic infections had underlying medical illness (diabetic mellitus or liver cirrhosis) and concurrent bacteremia, such conditions may predispose to a higher probability of hematogenous seeding. Recently, certain capsular serotypes and hypermucoviscosity phenotype of *K. pneumoniae* had been regarded to play a role in the development of metastatic infections. The potential role of K1 serotype was evidenced by a study that 12 of 14 *K. pneumoniae* isolates from Taiwanese patients with liver abscess and endophthalmitis were K1 serotype [41]. Moreover, the presence of hypermucoviscosity phenotype among *K. pneumoniae* isolates causing community-acquired bacteremia has been independently associated with a distinctive invasive syndrome, i.e., liver abscess, meningitis, pleural empyema or endophthalmitis [42]. The hypermucoviscosity phenotype was correlated to the presence of *rmpA*, and to destructive tissue abscess syndrome [43, 44].

Antimicrobial susceptibility of *K. pneumoniae* isolates in the present study showed uniform resistance to ampicillin, and all but one of the strains were susceptible to all cephalosporins. This is similar to the findings of published reports of community-acquired *K. pneumoniae* infections in Taiwan [19, 20, 31]. In other countries, there were more cephalosporin-resistant strains of *K. pneumoniae* infections because most of them were nosocomial origin [39, 45]. Since the majority of causative pathogens of cSSTIs in the community, including gram-positive cocci and *K. pneumoniae* were susceptible to cephalosporins and aminoglycosides, such a combination regimen can be the initial empiric therapy for patients with cSSTIs in Taiwan.

There were some limitations in the present study. First, only patients with microbiologically documented cSSTIs of the extremities were enrolled, while patients not undergoing surgical debridement or needle aspiration, or those with no bacterial growth in debrided tissues or aspirated pus, were not enrolled. Potentially, those with mild cSSTIs or prior antimicrobial therapy would be excluded. Second, we recruited patients with cSSTIs caused only by four target microorganisms, and those caused by other pathogens were arbitrarily ignored in the present study. In addition, because of the retrospective nature, clinical data in the medical records might be incomplete.

In conclusion, we highlight the role of *K. pneumoniae* in invasive soft-tissue infections involving extremities among individuals with underlying medical illnesses, especially liver cirrhosis, as well as its potential for gas and pus formation, and metastatic infections. Empiric antimicrobial coverage of *K. pneumoniae* and close monitoring of metastatic infections are mandatory in these patients.

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Conflicts of interests. The authors declare that they have no conflicts of interests.

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