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Risk factors for carbapenem non-susceptibility and mortality in *Acinetobacter baumannii* bacteremia in children

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SUMMARY

Objective: To examine the risk factors of carbapenem non-susceptibility and mortality among children with *Acinetobacter baumannii* bacteremia.
Methods: A retrospective chart review was conducted of 180 cases with *A. baumannii* bacteremia.
Results: The 30-day mortality risk of *A. baumannii* bacteremia was 26.1%. Carbapenem-non-susceptible *A. baumannii* was identified in 51.7% of cases. Logistic regression analysis indicated that prematurity, use of mechanical ventilation, and prior exposure to carbapenem antibiotics were independently associated with carbapenem-non-susceptible *A. baumannii* bacteremia, with adjusted odds ratios (aORs) and 95% confidence intervals (CIs) of 3.36 (1.17–9.65), 5.59 (2.24–13.97), and 2.97 (1.01–8.77), respectively. Further, carbapenem non-susceptibility, cancer-related neutropenia, organ dysfunction, admission to the intensive care unit, catheter-related bacteremia, and treatment with sulbactam-containing regimens were associated with mortality with aORs and 95% CIs of 4.76 (1.58–14.32), 4.54 (1.09–18.79), 25.95 (5.13–131.33), 3.53 (1.29–9.71), 0.25 (0.084–0.72), and 0.14 (0.046–0.45), respectively.
Conclusions: The majority of *A. baumannii* bacteremia was caused by carbapenem-non-susceptible strains with a high mortality rate. Carbapenem non-susceptibility, cancer-related neutropenia, the presence of organ dysfunction, and admission to an intensive care unit were associated with an increased mortality risk, whereas catheter-related bacteremia and treatment with a sulbactam-containing regimen were associated with decreased mortality among children with *A. baumannii* bacteremia.

1. Introduction

The recent emergence of multidrug-resistant Gram-negative enteric bacteria has become a major challenge to clinicians and endangers the health of patients worldwide.[1,2] *Acinetobacter baumannii* is among the most troublesome pathogens and has been implicated in several types of nosocomial infections due to its seemingly endless capacity to acquire antimicrobial resistance mechanisms.[3] In addition to its ability to acquire substantial resistance genes, its remarkable ability to adjust itself in the hospital environment, thus further enhancing its widespread transmissibility, has resulted in *A. baumannii* becoming a leading pathogen of nosocomial infection.[4] With the increase in the rate of carbapenem resistance in *A. baumannii* observed worldwide, it is becoming more and more difficult, if not impossible, to treat this pathogen due to our restricted pharmaceutical and therapeutic armamentarium. The existing literature provides substantial information regarding the epidemiology, clinical characteristics, and outcome of *A. baumannii* infection. However, most of the published studies have been conducted in the adult population, mainly from Western countries. Little information is available on the clinical outcome, antimicrobial susceptibility pattern, risk factors for carbapenem non-susceptibility, and risk factors for mortality of *A. baumannii* bacteremia in children in less developed settings. The objective of this study was to examine the clinical characteristics, outcomes, and antimicrobial susceptibility patterns of blood stream infection due to *A. baumannii* in hospitalized children.

Queen Sirikit National Institute of Child Health (QSNICH), generally known as the Children's Hospital, is a 426-bed, university-affiliated urban teaching hospital in Bangkok, Thailand, catering mainly to poor and underprivileged children. QSNICH provides all levels of care from primary to tertiary, and receives consultation and referral cases from neighboring provinces and nationwide. The hospital currently handles approximately 350 000 outpatient and 15 000 inpatient cases annually.

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2. Methods

The study was a retrospective case series analysis of children and adolescents aged 0–18 years receiving care at QSNICH between October 2005 and September 2010 with proven *A. baumannii* bacteremia. The cases were identified in the QSNICH Microbiology Laboratory database by searching for positive blood cultures. The medical records of the cases were obtained for the review from the medical record archives. Information on demographics, clinical outcomes, laboratory findings, and antimicrobial susceptibility patterns of the *A. baumannii* were collected. Patients were classified as having systemic inflammatory response syndrome (SIRS) based on the criteria proposed by Goldstein et al.[5]

A. baumannii were isolated and identified from clinical specimens by standard microbiological methods. Susceptibility testing of *A. baumannii* isolates was conducted using the standard disk diffusion method only. Antimicrobial agents included in the susceptibility testing for *A. baumannii* at QSNICH included amikacin, cefotaxime, ceftriaxone, ceftazidime, cefoperazone/sulbactam, ciprofloxacin, co-trimoxazole, gentamicin, imipenem, meropenem, netilmicin, and colistin. Ampicillin/sulbactam susceptibility was not part of routine susceptibility testing at our center due to the lack of Sensi-Disc. Susceptibility breakpoints were based on those defined by the Clinical and Laboratory Standards Institute (CLSI).[6] Carbapenem-non-susceptible *A. baumannii* was defined as isolates that exhibited in vitro resistance and/or intermediate resistance to imipenem and/or meropenem based on the disk diffusion method. Given the lack of current interpretative criteria for the disk diffusion testing of colistin against *A. baumannii*, modified zone criteria for colistin were used in this study in which susceptibility was determined by an inhibition zone size of $\geq$11 mm.[7,8]

2.1. Statistical analysis

Continuous variables were generally presented in terms of the mean and standard deviation. The median and interquartile range (IQR) was used when they were not normally distributed. Categorical variables were expressed as percentages. Comparisons between clinical and laboratory characteristics were done using the Student's *t*-test or Mann–Whitney test for continuous variables, as indicated, and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. To identify the independent risk factors of carbapenem non-susceptibility and mortality for *A. baumannii* bacteremia, multivariable logistic regression analyses using the backward likelihood ratio selection method were employed to control for the effects of potential confounding factors. A *p*-value of $\leq$0.05 was considered statistically significant.

3. Results

A total of 180 cases of *A. baumannii* bacteremia were identified among a total of 74 955 hospitalizations during the period between October 2005 and September 2010, or approximately 2.4 episodes per 1000 hospitalized children. The median age (IQR) was 4 (15.8) months. The male to female ratio was 1.25:1. Neonates and infants accounted for approximately three-quarters of the study population. The proportions of patients under 1 month, 12 months, and 24 months of age were 36.1%, 71.1%, and 86.1%, respectively.

3.1. Clinical characteristics

The baseline clinical and demographic characteristics of the study population are presented in Table 1. The infection occurred after a median (IQR) hospital stay of 8 (19.5) days. In all cases the infections were nosocomially acquired; 33.9% were acquired in intensive care units (ICU). Underlying diseases were identified in 145 cases (80.6%). Forty-four cases (24.4%) of *A. baumannii* bacteremia were considered to be the result of a contaminant rather than a causative pathogen of blood stream infection. Such cases were defined if there was an absence of clinical symptoms compatible with SIRS during the time when the organism was isolated from the blood. Of these 44 patients, 40 cases (90.9%) resolved spontaneously, and three cases (6.8%) were associated with intravascular catheterization.

Table 1
Characteristics of the study population

Characteristics (N = 180 unless otherwise specified)	n (%)
Median age (IQR), months	4 (15.82)
Male gender	100 (55.6)
Median length of hospital stay prior to bacteremia (IQR), days	8 (19.5)
Presence of any underlying disease	145 (80.6)
Prematurity/low birth weight	39 (21.7)
Congenital heart diseases	21 (11.7)
Malignancy	18 (10)
Congenital anomalies	13 (7.2)
Chronic lung disease	10 (5.6)
Chronic liver disease	8 (4.4)
Portal of entry (concomitant source of infection)	
Respiratory tract	31 (17.2)
Central venous catheter	43 (23.9)
Wound	8 (4.4)
Unknown	98 (54.4)
Presence of organ dysfunction	101 (56.1)
Presence of SIRS	136 (75.6)
Use of mechanical ventilator	81 (45)
Prior receipt of antibiotics	121 (67.2)
ICU admission	61 (33.9)
Polymicrobial infection	34 (18.9)
Median WBC count (IQR), $\times 10^9$/l	11.7 (12.225)
Carbapenem non-susceptibility (N =176)	91 (51.7)
Septic shock	50 (27.8)
30-day mortality	47 (26.1)
In-hospital mortality	51 (28.3)

ICU, intensive care unit; IQR, interquartile range; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.

3.2. Laboratory findings

The median (range) white blood cell count was 11.70 (0.13–96.09) $\times$ 10^9 cells/l. Despite the invasive nature of the illness, the white blood cell counts of 48.3% of the cases were considered to be within normal limits (5–15 $\times$ 10^9 cells/l). In other words, the sensitivity of this leukocyte count criterion in detecting *A. baumannii* bacteremia was only 51.7%. In addition, in a subgroup analysis of cases presenting with symptoms and signs compatible with SIRS, the sensitivity of this criterion remained rather low (60.4%).

A. baumannii was universally susceptible to colistin with a 100% susceptibility rate, followed by cefoperazone/sulbactam (63.9%), carbapenem (49.4%), amikacin (42.2%), and ceftazidime (40.6%). Of note, carbapenem non-susceptibility was identified in up to 51.7% of cases (n = 93). Factors associated with carbapenem non-susceptibility based on univariate and multivariable analysis are shown in Tables 2 and 3.

3.3. Clinical outcomes

Forty-three cases (23.9%) spontaneously resolved (defined by spontaneous defervescence plus negative blood culture prior to proper antibiotic treatment). In-hospital death occurred for a total

Table 2
Univariate analysis of the clinical characteristics of patients with *Acinetobacter baumannii* bacteremia with and without carbapenem non-susceptibility

Characteristics	Carbapenem susceptibility (N = 176), n (%)		
	Susceptible (n = 85)	Non-susceptible (n = 91)	p-Value
Median age (IQR), months	9 (28.86)	1 (7.57)	<0.001[a]
Male (n = 99)	51 (60)	48 (52.7)	0.332
Presence of underlying disease (n = 142)	63 (74.1)	79 (86.8)	0.033
Malignancy with febrile neutropenia (n = 18)	11 (12.9)	7 (7.7)	0.251
Prematurity (n = 39)	9 (10.6)	30 (33.0)	<0.001
Extremely low birth weight (n = 20)	3 (3.5)	17 (18.7)	0.002[b]
ICU admission (n = 61)	11 (12.9)	50 (54.9)	<0.001
SIRS (n = 134)	49 (57.6)	85 (93.4)	<0.001
Use of mechanical ventilation (n = 81)	13 (15.3)	68 (74.7)	<0.001
CABSI (n = 41)	8 (9.4)	33 (36.3)	<0.001
Polymicrobial bacteremia (n = 34)	17 (20)	17 (18.7)	0.825
Any organ dysfunction (n = 101)	30 (35.3)	71 (78.0)	<0.001
Cardiovascular dysfunction (n = 50)	11 (12.9)	39 (42.9)	<0.001
Respiratory dysfunction (n = 78)	20 (23.5)	58 (63.7)	<0.001
Neurological dysfunction (n = 39)	8 (9.4)	31 (34.1)	<0.001
Hematological dysfunction (n = 81)	21 (24.7)	60 (65.9)	<0.001
Renal dysfunction (n = 12)	3 (3.5)	9 (9.9)	0.071[b]
Hepatic dysfunction (n = 25)	8 (9.4)	17 (18.7)	0.025
Previous treatment with 3rd generation cephalosporin (n = 43)	18 (21.2)	25 (27.5)	0.331
Previous treatment with sulbactam[c] (n = 10)	1 (1.2)	9 (9.9)	0.019[b]
Previous treatment with penicillin (n = 21)	6 (7.1)	15 (16.5)	0.054
Previous treatment with aminoglycoside (n = 27)	9 (10.6)	18 (19.8)	0.091
Previous treatment with carbapenem (n = 36)	8 (9.4)	28 (30.8)	<0.001
Previous treatment with quinolone (n = 1)	0 (0)	1 (1.1)	1.0[b]
Abnormal WBC count (<5 or >15 × 10^9/l) (n = 93)	38 (44.7)	55 (60.4)	0.034
Median WBC count (IQR), × 10^9/l (n = 170)	10.890 (9.465)	12.670 (12.9025)	0.467[a]
Median hospitalization before bacteremia (IQR), days (n = 176)	4 (17)	10 (19)	<0.001[a]
Median length of stay (IQR), days (n = 176)	21 (55)	45 (70)	0.001[a]

CABSI, catheter-associated blood stream infection; ICU, intensive care unit; IQR, interquartile range; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.
[a] Mann–Whitney test.
[b] Fisher's exact test.
[c] Including cefoperazone/sulbactam or ampicillin/sulbactam.

of 51 cases (28.3%), but the 30-day mortality rate after an *A. baumannii* bacteremic episode was 26.1% (n = 47).

Eighty-five percent of cases who died within 30 days after the bacteremic episode had an underlying disease. The most common underlying chronic conditions among fatal cases were prematurity/low birth weight (27.7%), followed by congenital heart diseases (11.7%), malignancy (10%), and liver diseases (6.4%). The 30-day mortality rates among patients with *A. baumannii* bacteremia with an unidentified source, bacteremia with pneumonia, bacteremia with wound infection, and polymicrobial bacteremia were 31.9%, 44.7%, 4.3% and 27.7%, respectively.

3.4. Risk factors for severe disease

Univariate analysis indicated that neutropenic fever in children with underlying malignancy, extremely low birth weight, ICU admission, presence of SIRS, use of mechanical ventilation, presence of organ dysfunction, treatment with a carbapenem-containing regimen, treatment with a sulbactam-containing regimen (including cefoperazone/sulbactam and ampicillin/sulbactam), and carbapenem non-susceptibility were significantly associated with the 30-day mortality risk (Table 4). Logistic regression analysis revealed that carbapenem non-susceptibility, the presence of neutropenia in children with an underlying malignancy, organ dysfunction, ICU admission, catheter-related bacteremia, and treatment with a sulbactam-containing regimen were independently associated with mortality, with adjusted odds ratios and 95% confidence intervals of 4.76 (1.58–14.32), 4.54 (1.09–18.79), 25.95 (5.13–131.33), 3.53 (1.29–9.71), 0.25 (0.084–0.72), and 0.14 (0.046–0.45), respectively (Table 5).

Table 3
Logistic regression analysis of predictors of carbapenem non-susceptible *Acinetobacter baumannii* bacteremia

Predictors	aOR	95% CI	p-Value
SIRS	3.19	0.97–10.56	0.057
Use of mechanical ventilation	5.59	2.24–13.97	<0.001
Prematurity	3.36	1.17–9.65	0.024
Previous treatment with carbapenem	2.97	1.01–8.77	0.048
Previous treatment with sulbactam[a]	4.30	0.47–39.56	0.197
Catheter-associated blood stream infection	2.08	0.72–5.99	0.175

aOR, adjusted odds ratio; CI, confidence interval; SIRS, systemic inflammatory response syndrome.
[a] Including cefoperazone/sulbactam or ampicillin/sulbactam.

4. Discussion

Information on the burden of *A. baumannii* bacteremia in the pediatric population is virtually non-existent. Existing reports are mainly case reports and case series with relatively small sample sizes.[9] Our results showed that the burden of nosocomial *A. baumannii* bacteremia among children was rather comparable to that reported in the adult population in tertiary centers.[10] Similar to the existing literature, children with underlying debilitating chronic conditions were over-represented in this study, reflecting the opportunistic nature of this pathogen. This pathogen has been implicated in nosocomial blood stream infections particularly among those with an underlying debilitating chronic condition, with isolated bacteremia (bacteremia without an identifiable source) being the most common, followed by catheter-related blood stream infections and bacteremia with concurrent lower respiratory tract infections. In this study, we evaluated the performance of the white blood cell count as a screening tool

Table 4
Univariate analysis of predictors of mortality in *Acinetobacter baumannii* bacteremia

Characteristics	Mortality (N = 180), n (%)		
	Survived (n = 133)	Died (n = 47)	p-Value
Median age, months	4	4.3	0.626[a]
Male (n = 100)	69 (51.9)	31 (66.0)	0.095
Malignancy with febrile neutropenia (n = 18)	9 (6.8)	9 (19.1)	0.015
Prematurity (n = 39)	26 (19.5)	13 (27.7)	0.24
Extremely low birth weight (n = 20)	10 (7.5)	10 (21.3)	0.01
ICU admission (n = 61)	31 (23.3)	30 (63.8)	<0.001
SIRS (n = 136)	90 (67.7)	46 (97.9)	<0.001
Use of mechanical ventilation (n = 81)	45 (33.8)	36 (76.6)	<0.001
Catheter-associated blood stream infection (n = 43)	34 (25.6)	9 (19.1)	0.37
Polymicrobial bacteremia (n = 34)	21 (15.8)	13 (27.7)	0.074
Any organ dysfunction (n = 101)	56 (42.1)	45 (95.7)	<0.001
Cardiovascular dysfunction (n = 50)	11 (8.3)	39 (83.0)	<0.001
Respiratory dysfunction (n = 78)	33 (24.8)	45 (95.7)	<0.001
Neurological dysfunction (n = 39)	1 (0.8)	38 (80.9)	<0.001
Hematological dysfunction (n = 81)	40 (30.1)	41 (87.2)	<0.001
Renal dysfunction (n = 12)	2 (1.5)	10 (21.3)	<0.001
Hepatic dysfunction (n = 25)	11 (8.3)	14 (29.8)	<0.001
Carbapenem non-susceptibility (n = 91)	55 (41.4)	36 (76.6)	<0.001
Treatment with carbapenem-containing regimen (n = 74)	47 (35.3)	27 (57.4)	0.008
Treatment with sulbactam-containing regimen[b] (n = 51)	43 (32.3)	8 (17.0)	0.045
Treatment with colistin-containing regimen (n = 39)	29 (21.8)	10 (21.3)	0.94
Median hospitalization before bacteremia, days	9	8	0.263[a]

ICU, intensive care unit; SIRS, systemic inflammatory response syndrome.
[a] Mann–Whitney test.
[b] Including cefoperazone/sulbactam or ampicillin/sulbactam.

for *A. baumannii* bacteremia since little information is available in this regard. In addition, most of the studies in pediatric bacteremia have been conducted in children with community-acquired rather than nosocomial infections. Similar to studies by Bonsu et al. and Kuppermann et al.,[11,12] the total peripheral white blood cell count was a rather insensitive screening tool for bacteremia in children. Therefore, the decision to obtain blood cultures in children suspected of having bacteremia should not rely on this test.

A nationwide survey of more than 300 hospitals in the USA found that the rate of carbapenem resistance in *A. baumannii* increased from 9% in 1995 to 40% in 2004.[13] A more recent survey from the USA showed that this rate had increased to 49.2% in 2008.[14] In our study, the 51.7% rate of carbapenem-non-susceptible *A. baumannii* is comparable to the 54.5% carbapenem non-susceptibility rate reported in 2010 from the National Antimicrobial Resistance Surveillance Center, Thailand.[15] Previously identified risk factors for multidrug-resistant and/or carbapenem-non-susceptible *A. baumannii* invasive infection include recent ventilator-associated pneumonia due to carbapenem-non-susceptible *A. baumannii*,[16] the presence of excess intravascular devices,[16] ICU stay,[17–19] duration of hospital stay,[17] prior receipt and number of prescribed antibiotics,[20] prior treatment with a third-generation cephalosporin,[21] carbapenem,[19,21] or beta-lactam/beta-lactamase inhibitors,[19] previous colonization with *A. baumannii*,[20] and a recent invasive procedure.[20] Similar to existing reports, our study identified previous use of a carbapenem[19,22] and use of mechanical ventilation[18] as independent factors associated with carbapenem resistance. Further, we identified prematurity as being an independent risk factor for carbapenem-non-susceptible *A. baumannii* bacteremia.

Table 5
Logistic regression analysis of predictors of mortality in *Acinetobacter baumannii* bacteremia

Predictors	aOR	95% CI	p-Value
Carbapenem non-susceptibility	4.76	1.58–14.32	0.005
Cancer-related neutropenic fever	4.54	1.09–18.79	0.037
Presence of organ dysfunction	25.95	5.13–131.33	<0.001
ICU admission	3.53	1.29–9.71	0.014
Catheter-associated blood stream infection	0.25	0.084–0.72	0.011
Carbapenem-containing regimen	0.41	0.146–1.14	0.088
Sulbactam-containing regimen[a]	0.14	0.046–0.45	0.001

aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit.
[a] Including cefoperazone/sulbactam or ampicillin/sulbactam.

Limited data are available on the outcomes of *A. baumannii* bacteremia, especially that caused by multidrug-resistant and/or carbapenem-non-susceptible strains in the pediatric population. In addition, the mortality rate in *A. baumannii* bacteremia may not reflect the case fatality rate of *A. baumannii* bacteremia due to the presence of other contributing factors, especially underlying debilitating conditions such as extremely low birth weight neonates, congenital heart diseases, and cancer-related neutropenia. Nevertheless, the mortality rate among cases with *A. baumannii* bacteremia (26.1%) in our study is at the lower end of those reported for children and/or adults in Spain (34%)[10] and Korea (37.1%).[23] Various predictors of fatality have been reported, including age,[19] disseminated intravascular coagulation,[10] inappropriate or delayed antimicrobial treatment,[10,19] severity of organ failure,[16,19] and increased white blood cell count at bacteremia onset.[16] We found that the strongest risk factor for the 30-day mortality after *A. baumannii* bacteremia was the presence of one or more organ dysfunction. Further, cancer-related neutropenic fever and admission to the ICU each increased the mortality risk by an approximate factor of four. In parallel, evidence regarding the impact of multidrug resistance and/or carbapenem non-susceptibility on the mortality from *A. baumannii* bacteremia remains inconsistent. A few studies in hospitalized[22,24] and ICU[16,25] patients did not find a significant association between bacteremia caused by multidrug-resistant/carbapenem-non-susceptible *A. baumannii* and mortality. On the other hand, certain reports have shown multidrug-resistant *A. baumannii* infection to be associated with a poor outcome,[26–28] such as increased mortality,[18,19,27] higher hospitalization costs, and longer ICU and hospital stays.[27] Our results demonstrated that *A. baumannii* bacteremia caused by carbapenem-non-susceptible strains exhibited a 4.8-times higher risk of mortality

and a hospital stay twice the length of that of patients infected by susceptible strains.

In our study, a striking feature was the association between catheter-associated blood stream infection (CABSI) and a favorable outcome. More than 90% of cases with CABSI caused by *A. baumannii* had signs and symptoms compatible with SIRS. Approximately two-thirds of CABSI cases responded promptly to antibiotic treatment and 7.0% of cases resolved spontaneously after catheter removal. In addition, *A. baumannii* CABSI was also identified as a significant predictor of a lower mortality compared to non-CABSI. This finding may reflect the fact that the source of infection could be removed relatively easily compared to those who did not have any identifiable source or readily modifiable risk factor.

The high rate of resistance towards third-generation cephalosporins, beta-lactam/beta-lactamase inhibitors, and carbapenems is especially worrisome, as safe and effective therapeutic options may be extremely limited, if not unavailable. As of the end of 2010, none of our cases demonstrated colistin resistance. However, the reader should bear in mind that the method for testing colistin susceptibility was based on the disk diffusion method using the cut-off point zone size of $\geq$11 mm to indicate susceptibility. This method is not considered a gold standard; certain inconsistencies were found when this method was compared with minimum inhibitory concentration (MIC) measures based on standard agar dilution[29] and the Etest.[30,31]

A concurrent blood stream infection with other pathogens was not uncommon and was found in 18.8% of cases in our series compared to 27–35% reported from other studies.[32–34] Of note, such occurrences have not been described as being associated with a worse outcome or mortality in the present or previous reports on *A. baumannii* bacteremia.

In conclusion, carbapenem-non-susceptible strains were implicated in the majority of hospital-acquired *A. baumannii* bacteremia cases in children. Prematurity, the use of mechanical ventilation, and prior exposure to carbapenem antibiotics were the most important risk factors for carbapenem-non-susceptible *A. baumannii* bacteremia. Carbapenem non-susceptibility, cancer-related neutropenia, the presence of organ dysfunction, and ICU admission were risk factors for mortality among children with *A. baumannii* bacteremia. In contrast, catheter-related bacteremia and treatment with a sulbactam-containing regimen were associated with a decreased risk of mortality among these children.

Ethical approval: This study received ethical approval from Queen Sirikit National Institute of Child Health (IRB approval number 53-078).

Conflict of interest: No competing interest declared.

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