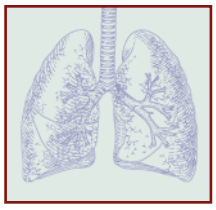

Respiratory Dysfunction in Patients With Sepsis: Protective Effect of Diabetes Mellitus

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Background Sepsis is a common complication in patients with diabetes mellitus. In a Western population, risk of respiratory dysfunction was lower in diabetic patients with sepsis.
Objective To compare organ dysfunction, particularly respiratory dysfunction, between sepsis patients with and without diabetes mellitus in an Asian population.
Method Hospital discharge data were collected for the period 2004 through 2008. Patients with sepsis, diabetes mellitus, and organ dysfunction were identified by using the *International Statistical Classification of Diseases and Related Health Problems, 9th Revision, Australian Modification* codes.
Results Of the 383 238 patients hospitalized during the 5 years, 2943 of the 9221 who had sepsis also had diabetes (31.9%). The most common organ dysfunctions in patients with sepsis were renal (31.5%), cardiovascular (19.2%), and respiratory (10.9%). Among patients with sepsis, respiratory dysfunction was less likely in patients with diabetes (9.4%) than in those without (11.6%; $P = .002$), but renal dysfunction was more likely in patients with diabetes (46.5%) than in those without (24.4%; $P < .001$). However, only 27.6% of patients with diabetes had a respiratory source of sepsis compared with 33.4% in patients without diabetes ($P < .001$). Among patients with sepsis, diabetes mellitus was a significant and independent predictor of respiratory dysfunction (odds ratio, 0.80; 95% confidence interval, 0.66-0.98) after adjustments for age, sex, ethnicity, admission to intensive care, number of comorbid conditions, and other infection sources.
Conclusion Among an Asian population, respiratory dysfunction in patients with sepsis is less likely to develop in those with diabetes than in those without diabetes. (*American Journal of Critical Care.* 2011;20:e41-e47)

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Epidemiological studies have shown that sepsis is a common health care problem. In the United States, approximately 700 000 cases occur each year, and the cost of care is almost US$17 billion.[1,2] In Singapore, sepsis has accounted for about 2.3% of all hospital admissions.[3] Sepsis often occurs in patients with diabetes mellitus, and diabetes mellitus is associated with marked morbidity and mortality.[1,2,4] Sepsis complicated by acute organ system dysfunction accounts for almost half of intensive care unit (ICU) resources and is associated with a higher morbidity and mortality than sepsis without acute organ system dysfunction.[2,5,6] Thus, accurate identification of populations at risk for acute organ dysfunction is crucial to improve understanding of the mechanisms involved in the risk and to develop novel therapies for these patients.

Clinical and epidemiological studies[6-9] have indicated that respiratory dysfunction is less likely in patients who have both sepsis and diabetes mellitus than in patients who have sepsis but no diabetes. Possible explanations for this difference include the effects of hyperglycemia on the inflammatory response, metabolic abnormalities in diabetes, and interactions of agents used to treat diabetes mellitus.[7,9] Compared with other ethnic groups, Asian patients, especially those from South Asian countries, have a 4- to 6-fold greater risk for type 2 diabetes mellitus and a higher risk for renal, cardiovascular, and cerebrovascular complications.[10] Knowledge of differences in the pattern of organ failure would be useful in monitoring and managing patients with diabetes mellitus in whom sepsis develops. However, little information is available on sepsis and organ dysfunction in Asian patients with diabetes.

The purpose of the study reported in this article was to compare the patterns of organ dysfunction, particularly respiratory dysfunction, between Asian patients with sepsis who did or did not have diabetes mellitus.

Methods

Data Collection

Singapore General Hospital is the largest acute tertiary care hospital in Singapore. With 1600 beds, it serves approximately one-fourth of Singapore's population of 4.98 million people.[11] Each year the hospital handles approximately 80 000 patient discharges. Data on all hospitalized patients 18 years or older, from January 1, 2004, to December 31, 2008, were collected from the hospital's data warehouse, Information Technology Department, Singhealth Group. The data included demographic information such as ethnicity, sex, age, and marital status and clinical characteristics such as dates of admission and discharge, dates of ICU admission and discharge, up to 10 *International Statistical Classification of Diseases and Related Health Problems, 9th Revision, Australian Modification* (*ICD-9-AM*) diagnosis codes, up to 10 *ICD-9-AM* procedure codes, discharge status, and disposition at discharge. The research protocol was approved by the ethics committee of Singapore General Hospital, and no informed consent was required.

> Patients from South Asian countries have a 4-6 times greater risk of type 2 diabetes mellitus.

Case Definition

Sepsis was defined[1,3] as the presence of any of the *ICD-9-AM* codes listed in Table 1. In previous validation studies,[1,12] this method had positive predictive values of 88.7% to 99.8% for identifying true cases of sepsis. Diabetes mellitus was defined by *ICD-9-AM* code 250, which has a positive predictive value of 95%.[13]

Organ dysfunctions, type of organ dysfunction, source of infection (ie, the anatomical site of infection, which included respiratory; genitourinary; skin, soft tissue, or bone; gastrointestinal; central nervous system; cardiovascular; and others), and associated surgical and medical conditions were defined by using a combination of *ICD-9-AM* diagnosis, diagnostic codes and procedure codes[1,2,14] (Table 2). Chronic comorbid conditions were identified and were used to calculate the well-established adaptation of the Charlson Comorbidity Index by Deyo et al.[15]

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Table 1
Codes from the *International Statistical Classification of Diseases, Ninth Revision, Australian Modification*, used to define sepsis

Code	Description
038.0	Streptococcal septicemia
038.1	Staphylococcal septicemia
038.2	Pneumococcal septicemia
038.3	Septicemia due to anaerobes
038.4	Septicemia due to other gram-negative organisms
038.8	Other specified septicemias
0038.9	Unspecified septicemia
003.1	Salmonella septicemia
020.2	Septicemic plague
022.3	Anthrax septicemia
036.2	Meningococcal septicemia
036.3	Waterhouse-Friderichsen syndrome
054.5	Herpetic septicemia
098.89	Gonococcemia
112.5	Systemic candidiasis
995.91	Systemic inflammatory response syndrome due to infectious process without organ dysfunction
995.92	Systemic inflammatory response syndrome due to infectious process with organ dysfunction
785.52	Septic shock

Statistical Analysis

Categorical variables were reported as percentages and continuous variables as means with standard deviations. Because of their skewed distribution, length of hospital stay and the number of comorbid conditions were summarized by using geometric means with 95% confidence intervals. Among patients with sepsis, variables were compared between those with and without diabetes mellitus by using χ^2 tests, 2-tailed t tests, and Mann-Whitney tests as appropriate. Logistic regression was used to assess the association of respiratory dysfunction with diabetes mellitus, and adjustments were made for age, sex, ethnicity, ICU admissions, number of comorbid conditions, and the source of infection. The Hosmer-Lemeshow χ^2 goodness-of-fit test was used to exclude nonsignificant variables and to identify clinically plausible interaction terms. The area under the receiver operating characteristic curve was also presented for the regression model. All P values were 2 sided. The level of significance was set at the conventional level of $\alpha = .05$. STATA, version 10.0 (StataCorp LP, College Station, Texas) was used for all data analysis.

Presence of diabetes mellitus was negatively associated with respiratory dysfunction.

Results

Of the 383 238 patients 18 years and older hospitalized during the period 2004 through 2008, a total of 9221 (2.4%) met the criteria used to define sepsis. Among the patients with sepsis, 2943 (31.9%) had diabetes mellitus. The patients with diabetes were generally older (mean 65.5 years; SD, 12.4) than those without diabetes (59.8 years; SD, 17.4; $P < .001$) and were predominately women (53% vs 48.5%; $P < .001$). The percentage of patients managed medically did not differ significantly ($P = .87$) between those with both sepsis and diabetes (66.5%) and those with sepsis only (66.7%). The percentage of patients who received ICU care also did not differ significantly ($P = .28$) between those with both sepsis and diabetes (16.5%) and those with sepsis only (17.4%). Patients with both sepsis and diabetes had significantly more comorbid conditions than did patients with sepsis only (geometric mean, 1.9 vs 1.3; $P < .001$). The demographic profile, clinical characteristics, and outcomes of patients with sepsis are given in Table 3.

Patients with both sepsis and diabetes had a significantly lower frequency than did patients with sepsis only for respiratory (27.6% vs 33.4%), gastrointestinal (25.5% vs 29.3%), cardiovascular (0.7% vs 1.9%), and neurological (0.8% vs 1.4%) sources of infection (Figure 1). However, patients with both sepsis and diabetes had an increased frequency of renal (32.6% vs 26.2%); skin, soft tissue, or bone (15.6% vs 13.1%); and other (19% vs 15.1%) sources of infection.

Among all patients with sepsis, 10.9% had respiratory dysfunction, 31.5% had renal dysfunction, 19.2% had cardiovascular dysfunction, 11.8% had hematological dysfunction, and 7.6% had other organ dysfunction (Figure 2). Patients with both sepsis and diabetes were more likely than those with sepsis only to have renal (46.5% vs 24.4%) and metabolic (4.7% vs 3.6%) dysfunction and less likely to have respiratory (9.4% vs 11.6%), hepatic (1.1% vs 1.7%), and hematologic (9.4% vs 12.9%) dysfunction. The occurrence of other organ dysfunctions differed little between the 2 groups.

Multivariate logistic regression analysis showed that diabetes mellitus was significantly negatively associated with respiratory dysfunction (adjusted odds ratio, 0.80; 95% confidence interval, 0.66-0.98; $P = .03$) after adjustments were made for age, sex, ethnicity, ICU admission, number of comorbid conditions, and infection sources, including respiratory; genitourinary; skin, soft tissue, or bone; and gastrointestinal sources (Table 4). The goodness of fit of the regression model was assessed by using

the Hosmer-Lemeshow test ($\chi^2_8 = 8.3$; $P = .40$). The area under the receiver operating characteristic curve was 0.92 ($P < .001$).

Evaluation of hospital mortality and length of stay (Table 3) indicated that sepsis patients with and without diabetes mellitus had comparable hospital mortality (19.2% vs 20.0%; $P = .37$). This finding was evident in the subgroup of patients with respiratory dysfunction as well (56.7% vs 52.9%; $P = .29$). Similarly, the hospital length of stay did not differ significantly between the 2 groups (geometric mean, 12.1 days vs 12.2 days; $P = .53$) or in the subgroup of patients with respiratory dysfunction (15.9 days vs 17.8 days: $P = .21$).

Discussion

In this study of 5 years of discharge data from a major tertiary acute care hospital, we found that respiratory dysfunction was less likely to develop in patients with both sepsis diabetes mellitus than in patients with sepsis only. This difference persisted even after adjustments were made for age, sex, ethnicity, ICU admission, the number of comorbid conditions, and the source of infection.

Our study was the first on the effect of diabetes mellitus on respiratory dysfunction in an Asian population, and our results confirm and extend the previous published results for a Western population.[9] In an observational cohort study[6] of 375 patients treated with mechanical ventilation for more than 48 hours, higher glucose levels in the first 24 hours of respiratory failure were associated with a decreased risk for acute respiratory distress syndrome (ARDS; $P = .025$). In another large cohort of 688 critically ill patients at risk for ARDS from sepsis, trauma, massive transfusion, and aspiration, diabetes protected against the development of ARDS, even after adjustments for potential confounders such as age, clinical risk for ARDS, severity of illness, and transfusion (adjusted odds ratio, 0.58; 95% confidence interval, 0.36-0.92).[16] In a third independent cohort study[17] of 160 patients with sepsis, diabetes mellitus was detected in only 24% of patients with acute lung injury, the less severe form of ARDS, and in 43% of patients without acute lung injury ($P = .01$). Investigators in other clinical trials[8,18] have also reported reduced occurrence of ARDS or acute lung injury in sepsis patients with diabetes mellitus. Furthermore, in a large epidemiological study involving 12.5 million sepsis cases from the US National Hospital Discharge Survey from 1979 to 2003, Esper et al[7] found that patients with diabetes mellitus were less likely to have acute respiratory failure than were patients without diabetes (9% vs 14%; $P < .05$) and were more likely to have acute renal failure (13% vs 7%; $P < .05$). The reduced likelihood of respiratory dysfunction in the patients with diabetes mellitus occurred irrespective of the source of infection.

Our results and these published findings support the view that respiratory dysfunction is less likely to develop in patients with sepsis and diabetes mellitus than in patients with sepsis only. Nevertheless, the results of 2 studies contradict this finding. In a large population-based case-control study[19] and a cohort study,[20] the risk of pneumonia-related hospitalizations and deaths was increased in patients with type 2 diabetes.

Table 2
Diagnosis/procedure codes from the *International Statistical Classification of Diseases, Ninth Revision, Australian Modification*, used to define organ dysfunction

Respiratory dysfunction	
96.04	Endotracheal intubation (emergency procedure)
96.71	Ventilator management (<96 h)
96.72	Ventilator management (>96 h)
518.81	Respiratory failure (acute)
518.82	ARDS
518.85	ARDS following shock/trauma
799.1	Respiratory arrest
Cardiovascular dysfunction	
458.0	Postural hypotension
458.8	Hypotension, specified type, NEC
458.9	Hypotension, arterial (constitutional)
785.5	Shock
785.51	Cardiogenic shock
785.59	Circulatory shock, septic shock
Hepatic dysfunction	
570	Acute hepatic failure/necrosis
572.2	Hepatic encephalopathy
573.3	Hepatitis (septic and NEC)
Renal dysfunction	
39.95	Hemodialysis
580.*x*	Acute glomerulonephritis
584.*x*	Acute renal failure
586	Renal shutdown, renal failure NOS
Hematologic dysfunction	
286.6	Purpura fulminans
286.9	Coagulopathy
287.4–5	Thrombocytopenia (primary, secondary, NEC)
790.92	Abnormal coagulation profile
Metabolic dysfunction	
276.2	Acidosis (lactic or metabolic NEC)
Neurological dysfunction	
348.1	Anoxic brain damage
348.3	Encephalopathy, acute
780.01	Coma
780.09	Altered consciousness, NEC

Abbreviations: ARDS, acute respiratory distress syndrome; NEC, not elsewhere classified; NOS, not otherwise specified.

Patients with sepsis and diabetes mellitus are less likely to develop respiratory dysfunction than those without diabetes mellitus.

Table 3
The demographics, clinical characteristics, and outcomes of patients with sepsis

	Sepsis without diabetes mellitus (n = 6278)	Sepsis with diabetes mellitus (n = 2943)
Age,[a] mean (SD), y	59.8 (17.4)	65.5 (12.4)
Female sex,[b] % of patients	48.5	52.8
Ethnicity,[b] % of patients		
Chinese	78.2	65.6
Malay	10.8	19.3
Indian	5.2	11.2
Other	5.8	3.8
Medical condition, % of patients	66.7	66.5
Surgical condition, % of patients	33.3	33.5
Admission to intensive care unit, %	17.4	16.5
No. of comorbid conditions,[c] geometric mean (95% confidence interval)	1.3 (1.3-1.4)	1.9 (1.9-2.0)
Organ failures,[b] % of patients		
1	25.9	37
2	9.9	13.1
≥3	8.8	8.5
Hospital mortality, % of patients	20.0	19.2
Hospital length of stay, days, geometric mean (95% confidence interval)	12.2 (11.8-12.5)	12.1 (11.7-12.5)

[a] $P < .001$ by 2-sample t test.
[b] $P < .001$ by χ^2 test.
[c] $P < .001$ by Mann-Whitney test.

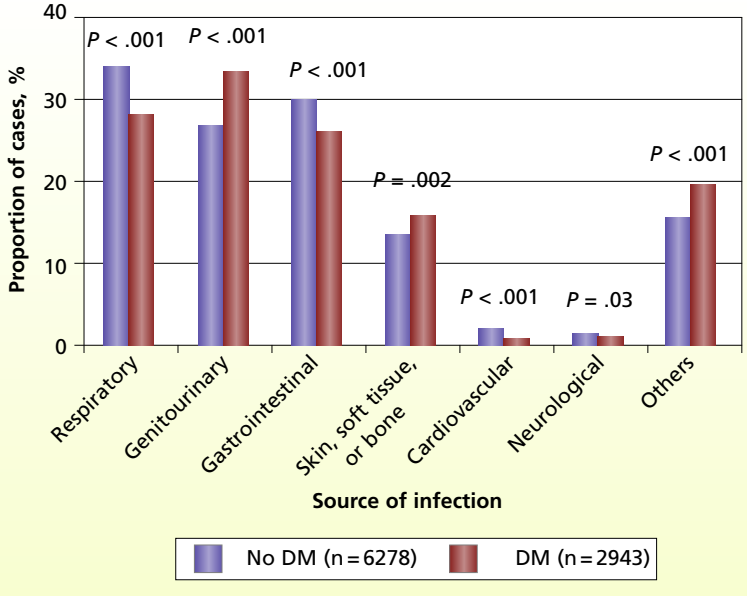

Figure 1 Sources of infection in sepsis patients with and without diabetes mellitus (DM).

*$P < .05$. ** $P < .01$ by χ^2 test.

These contradicting study results emphasize that the underlying mechanism for the effect between diabetes mellitus and respiratory dysfunction is still not well understood.

Neutrophils play an essential role in the host inflammatory response against infection.[21] Neutrophils from patients with diabetes can have impaired biological responses, including reduced bactericidal activity and impaired chemotaxis.[22,23] Compared with neutrophils from age and sex-matched controls, neutrophils from patients with diabetes adhere with less affinity to endothelial cell monolayers.[24,25] In addition, neutrophils from diabetic patients produce 40% less leukotriene B4 than do neutrophils from healthy volunteers.[26] Also, neutrophils from uninfected patients with poorly controlled diabetes did not have the same bactericidal activity as did neutrophils from healthy volunteers or patients with well-controlled diabetes.[23] Furthermore, defects of neutrophil chemotactic, phagocytic, and microbicidal activities in experimental studies in diabetic rats and mice have been reported.[21,27] These abnormalities in neutrophil function may protect the lungs by decreasing the ability of the neutrophils to migrate into the organ and to produce oxidant damage. Impaired neutrophil function or altered neutrophil-endothelial interactions have been proposed as a possible mechanisms for reduced incidence of respiratory dysfunction.[22,23]

Likewise, hyperglycemia can have immunomodulatory effects. Hyperglycemia in itself has an independent effect on neutrophil and endothelial properties, resulting in decreased injury in response to endotoxin.[22] In an in vitro study,[28] hyperglycemia increased production of anti-inflammatory cytokines such as interleukin 10 and promoted mitochondrial dysfunction. Impaired neutrophil function resulting in decreased intracellular bactericidal activity, opsonic activity, and innate immunity has also been reported.[29] Such effects could theoretically modulate the intense inflammation associated with respiratory organ dysfunction and may explain the decrease in respiratory dysfunction, but what the effects contribute to the increased incidence of other organ dysfunctions, such as renal failure, is not known. Further studies on these differential effects are needed.

From the clinical perspective, the development of organ failures determines the course and prognosis of most sepsis patients. Patients who usually die of sepsis in the course of different comorbid conditions have their deaths attributed to these conditions rather than to sepsis. Among specific organ dysfunctions, respiratory dysfunction is the most common, and then, in order, cardiovascular and renal failure.

The finding that patients with both sepsis and diabetes are less likely than patients with sepsis only to have respiratory dysfunction and more likely to have renal failure will have a significant impact on the management of sepsis patients. The effect of diabetes in patients with sepsis will be augmented by the increasing incidence of diabetes among Asian patients.[30] It would affect the need of support systems and equipment resource in ICUs and high-dependence units where sepsis patients receive care. The effect of diabetes could also be a prognostic indicator in patients with sepsis.

Our study had several limitations. The advantages of hospital discharge data are well known. The data are relatively inexpensive to obtain and use, are more reliable than other sources of data, cover a large population over multiple years, and are being used extensively in health services and health policy research.[31] Nevertheless, hospital discharge data are administrative and are not intended for research purposes. The data are subject to coding errors and omissions of important diagnoses and complications, conditions that could have affected our results.[32] However, the coding errors might occur across all patient groups, a possibility that offsets the possible impact of the errors. Although detailed chart reviews could provide more reliable data, chart reviews are time-consuming and labor intensive.[33]

The data we used were generated from a single, large acute care tertiary hospital, a situation that limits the generalizability of our results. Furthermore, lack of data on patients' medication history and/or duration of existing comorbid conditions might affect the interpretation of the results. Another possible confounding variable is chronic alcohol abuse, which may increase the incidence of ARDS in critically ill patients.[23] Unfortunately, we do not have the alcohol intake history of all patients whose data were used in our study.

In conclusion, our results confirm and extend the results of other studies done in Western populations, suggesting that in this group of Asian patients, respiratory dysfunction is also less likely to develop in patients with both sepsis and diabetes mellitus than in patients with sepsis only.

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Y. Yang designed and performed the study and contributed to the analysis of data, interpretation of data, and writing of the final draft of the manuscript. Z.H. Abdul-Salam contributed to the study design, the analysis of data, and contributed to the manuscript. B.C. Ong contributed to the study design, the analysis of data, and the writing of the manuscript. K.S. Yang contributed to the study design, the analysis of data, and the manuscript.

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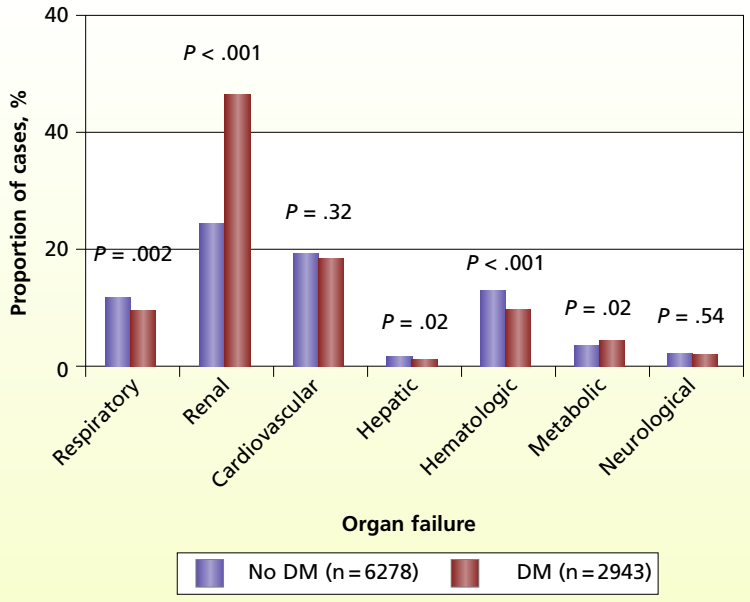

Figure 2 Frequency of organ dysfunction in sepsis patients with and without diabetes mellitus (DM).

*$P < .05$. ** $P < .01$ by χ^2 test.

Table 4
Regression analysis assessing associations of factors with respiratory organ failure in patients with sepsis (N = 9221)[a]

Factor	*b*	Odds ratio	95% confidence interval of odds ratio	*P*
Age group, y				
18-54	Reference			
55-64	0.25	1.28	1.01-1.63	.04
65-74	0.21	1.23	0.96-1.56	.10
75-84	0.41	1.50	1.14-1.98	.004
>85	0.90	2.47	1.61-3.76	<.001
Male sex	0.11	1.11	0.93-1.33	.24
Ethnicity				
Chinese	Reference			
Malay	-0.09	0.91	0.69-1.19	.50
Indian	0.11	1.11	0.78-1.59	.56
Others	0.08	1.09	0.76-1.55	.64
Admission to intensive care unit	3.24	25.58	21.14-30.95	<.001
Surgery vs medical	1.33	3.79	3.14-4.58	<.001
No. of comorbid conditions	-0.02	0.98	0.89-1.08	.63
Diabetes mellitus	-0.22	0.80	0.66-0.98	.03
Infection source				
Respiratory	1.20	3.30	2.77-3.95	<.001
Genitourinary	-0.36	0.70	0.57-0.87	.001
Skin, soft tissue, or bone	-0.31	0.73	0.56-0.95	.02
Gastrointestinal	-0.21	0.81	0.67-0.98	.03

[a] Logistic regression was used for analysis. Hosmer and Lemeshow test, $P = .40$. Area under the receiver operating characteristic curve, 0.92; $P < .001$.

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FINANCIAL DISCLOSURES
None reported.

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